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REVIEW

Multifaceted functions of tissue-resident memory T cells in tumorigenesis and cancer immunotherapy

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Abstract

Tissue-resident memory T (T_{RM}) cells are well reported as a strong protective first line of defense against foreign antigens in non-lymphoid tissues. Moreover, T_{RM} cells have demonstrated critical protective roles in antitumor immunity, contributing to enhanced survival and tumor growth inhibition across various cancer types. However, surprisingly, recent studies suggest that T_{RM} cells can exhibit paradoxical effects, potentially promoting tumor progression under certain conditions and leading to adverse outcomes during antitumor immune responses. Understanding the complexities of T_{RM} cell functions will enable us to harness their potential in advancing cancer immunotherapy more effectively. Therefore, this review comprehensively investigates the dual roles of T_{RM} cells in different tumor contexts, highlighting their protective functions in combating cancers and their unfavorable potential to exacerbate tumor development. Additionally, we explore the implications of T_{RM} cell behaviors for future cancer treatment strategies, emphasizing the need for further research to optimize the therapeutic exploitation of T_{RM} cells while mitigating their deleterious effects.

Keywords Tumor-infiltrating lymphocytes (TILs) · Tissue-resident memory T (T_{RM}) cells · Tumorigenesis · Cancer immunotherapy · $CD103^+$ lymphocytes

Introduction

Tissue-resident memory T (T_{RM}) cells represent a specialized subset of memory T (T_{MEM}) cells that remain permanently localized within peripheral non-lymphoid tissues (NLTs). These cells are strategically positioned to provide an immediate and robust immune response upon re-exposure to previously encountered pathogens [1–4]. Thus, T_{RM} cells are present in various NLTs, including the lungs [5, 6], skin [7, 8], brain [9, 10], gut [11, 12], and other NLTs [13, 14].

T_{RM} cell development is initiated when naive T (T_N) cells differentiate into effector T cells upon activation by antigen-presenting cells (APCs) exhibiting antigenic fragments. The activated effector T cells subsequently migrate from secondary lymphoid organs, including lymph nodes and spleen, to the inflamed site, where certain cell types undergo further differentiation into T_{RM} cells [15, 16]. The T_{RM} cells remain in the NLTs due to the decreased expression of the cell-surface molecules such as sphingosine-1-phosphate receptor 1 (S1PR1), CC-chemokine receptor 7 (CCR7), and L-selectin (CD62L), which are typically involved in T cell migration from NLTs [17–19]. Furthermore, the T_{RM} cells exhibit elevated tissue residency molecule expressions, such as CD69, CD103, and CD49a [20–22]. CD69 mainly parks T_{RM} cells in the tissue by interfering with S1PR1 [21–23], and CD103 facilitates the anchoring of T_{RM} cells to epithelial cells by binding to E-cadherin [21, 22]. CD49a interacts with collagen IV, which promotes the adhesion of T_{RM} cells to the extracellular matrix (ECM) [22].

T_{RM} cells are not only responsible for immune protective responses in NLTs throughout the body, including the gut, skin, respiratory system, and central nervous system [16, 24–26], but they also play a significant role in the detection and elimination of cancer cells. For instance, cytotoxic $CD8^+$ T_{RM} cells are known to detect tumor cells; meanwhile, tumor-infiltrating lymphocytes (TILs) have been found to exhibit significant tissue-resident memory properties, suggesting that TILs predominantly comprise T_{RM} cells [21, 27]. Moreover, the inhibition of T_{RM} cell generation has been shown to impair the ability to suppress

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transplantable melanoma in mice [28]. However, some studies have revealed that excessive or dysregulated T_{RM} cell activity contributes to inflammatory diseases such as multiple sclerosis, autoimmune disorders, including type 1 diabetes and vitiligo, and long-term complications following infections and organ transplantation [14, 29–32]. Furthermore, several studies have revealed that tumor-infiltrating T_{RM} cells may perform adverse roles, such as contributing to immune-related adverse events (irAEs), rather than solely protecting the host, particularly during therapeutic treatment using immune checkpoint inhibitors (ICIs) [33, 34].

Therefore, this review explores the dual roles of tumor-infiltrating T_{RM} cells across various tissues, highlighting their protective functions and potential contribution to adverse outcomes in tumor progression.

General features of tumor-infiltrating TRM cells

Tumor-infiltrating T_{RM} cells exhibit several unique characteristics, including the expression of specific surface markers and transcription factors that distinguish them from other T cell subsets. For instance, tissue residency markers such as CD69, CD103, and CD49a are expressed at higher levels in tumor-infiltrating T_{RM} cells than those observed in T_{RM} cells from healthy tissues [35]. CD103 facilitates adhesion to E-cadherin on normal epithelial cells and epithelial tumor cells [36–38]. The interactions of these tissue residency markers facilitate the localization of T_{RM} cells within the tumor microenvironment (TME), playing a pivotal role in regulating tumor growth [39, 40]. In addition, tumor-infiltrating T_{RM} cells exhibit upregulation of four transcription factors: Blimp-1, Hobit, Notch, and Runx3 [35, 41–43]. Blimp-1 and Hobit are essential for generating and maintaining T_{RM} cells [44, 45]. Notch signaling additionally plays a role in sustaining T_{RM} cell populations and regulating their cytokine production [36, 46]. Runx3 is crucial in differentiating and upregulating tissue residency markers on T_{RM} cells [41, 47]. Tumor-infiltrating T_{RM} cells also exhibit upregulation of immune checkpoint receptors such as programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte associated protein 4 (CTLA-4), lymphocyte activation gene 3 (LAG-3), T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) and T cell immunoglobulin and mucin domain 3 (TIM-3) [35, 48–51]. These immune checkpoint receptors are essential for maintaining self-tolerance and preventing autoimmunity by regulating T cell activity [52, 53]. However, alternatively, tumor cells induce exhaustion of T_{RM} cells through interactions with various immune checkpoint ligands. Specifically, PD-L1 and/or PD-L2 proteins on tumor cells engage with PD-1 on T_{RM} cells to promote inhibitory signaling [54]. Similarly, CD155 and/or CD112 on tumor cells bind to TIGIT on T_{RM} cells, contributing to immune suppression [55]. Galectin-9 (GAL-9), a ligand for TIM-3, also binds to TIM-3 on T_{RM} cells, further driving their exhaustion [56]. Furthermore, T_{RM} cells are regulated by interactions between the major histocompatibility complex (MHC) class II subgroup and LAG-3, as well as CD80/86 with CTLA-4, which collectively suppress the cytotoxic functions of T_{RM} cells, facilitating tumor immune cell evasion [57, 58]. In addition to these inhibitory receptors, 4-1BB, a costimulatory molecule crucial for enhancing T cell proliferation and survival, is upregulated on tumor-infiltrating T_{RM} cells, further contributing to their activation potential within the TME [35, 59–61]. While these distinctions are notable, the differences between tumor-infiltrating T_{RM} cells and their counterparts in healthy tissues remain less thoroughly explored and require further investigation.

Protective role of TRM cells in cancer studies

Although the identification of cancer can be traced back several millennia, effective and universally successful methods for its prevention and treatment remain elusive. Consequently, cancer continues to result in significant mortality annually, both directly and through associated complications [62]. Therefore, the critical need for advancements in cancer treatments has been emphasized, leading to the development and proposition of numerous therapeutic approaches; for example, commonly employed cancer therapies, including radiotherapy and chemotherapy, using agents such as arsenic compounds and nitrogen mustards [63–66]. However, radiotherapy is known for its capacity to inadvertently damage healthy tissues in addition to targeting tumors, and both arsenic compounds and nitrogen are known for their high toxicity levels. For these reasons, a recent focus on cancer treatment has been developing and applying immunotherapy. This therapeutic strategy harnesses the body's immune system to recognize and combat cancer cells. A key area of investigation in cancer immunotherapy currently focuses on T cells, lymphocytes that are integral to the adaptive immune system, which explores their potential to combat malignancies [67]. Tumor-specific $CD8^+$ T cells are induced by cytokines such as interferon (IFN)-α, IFN-β, and interleukin (IL)-12, leading to the production of potent antitumor molecules, including tumor necrosis factor (TNF)-α, as well as cytotoxic granzymes (GZMs) and cytolytic perforin. The coordinated release of these molecules and proinflammatory cytokines, such as IFN-γ, effectively mediates the destruction of malignant cells [41, 59, 68].

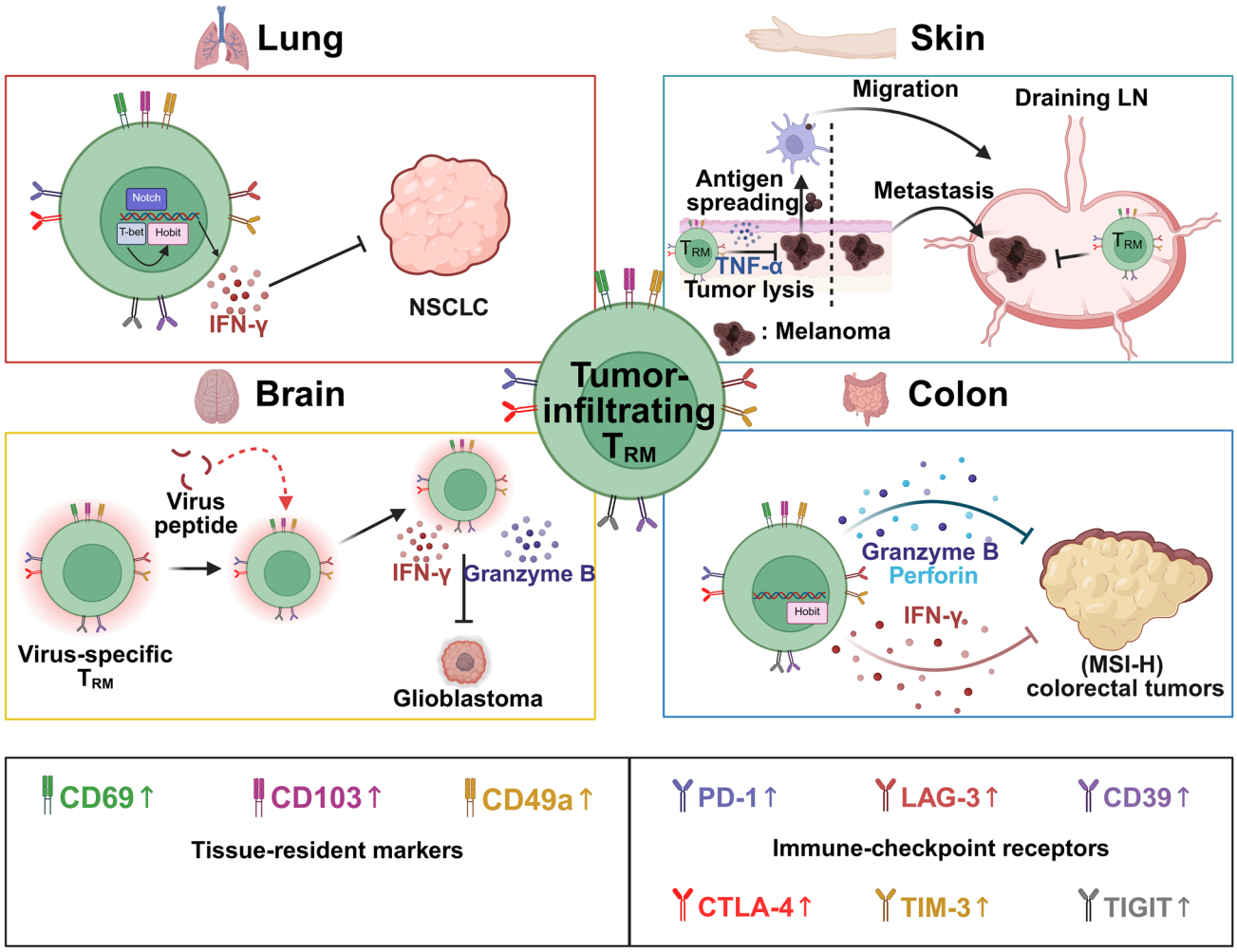

Fig. 1 Protective role of tissue-resident memory T (T_{RM}) cells across various tissues, including lung, skin, brain, and colon. In the lung, T_{RM} cells expressing Notch, T-bet, and Hobit produce interferon-gamma (IFN-γ), which contributes to antitumor immunity and plays a protective role against non-small cell lung cancer (NSCLC) progression. T_{RM} cells amplify antitumor immunity in the skin by TNF-α and triggering antigens that spread through dendritic cells (DCs). Furthermore, T_{RM} cells in draining lymph nodes (LNs) regulate metastasis by providing long-term immunity. In the brain, virus-specific T_{RM} cells release IFN-γ and granzyme B in response to viral peptides, promoting cytotoxic effects on tumor cells and potentially supporting protective immunity against glioblastoma. In the colon, T_{RM} cells expressing Hobit produce IFN-γ, granzyme B, and perforin, which enhance protective antitumor immunity within colorectal tumors and may also target microsatellite instability-high (MSI-H) colorectal tumors

Moreover, the current medical field has highlighted that treatment with immune checkpoint inhibitors enhances the cytotoxic function of TILs against tumor growth [69–73]. Recent studies have demonstrated that among immunotherapies, T_{RM} cells play a pivotal role in enhancing the efficacy of immunotherapy due to their potent cytotoxic functions, localized tissue residency, and rapid antigen-responsive capabilities [74–77]. Thus, in the following section, we summarize the protective roles of T_{RM} cells against cancer development/growth in various tissues (Fig. 1).

Protective roles of TRM cells in lung cancer

Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer, accounting for approximately 85% of all cases [78, 79]. Lung tumor-infiltrating T_{RM} cells are distinguished from other T cell subsets by the elevated expression of immune checkpoint molecules, including LAG-3, PD-1, TIM-3, CTLA-4, CD39, and TIGIT [35, 80, 81]. Additionally, these cells are characterized by a lower expression of the activation marker KLRG1 [35, 36]. Several studies have demonstrated that T_{RM} cells play a protective role against lung cancer [48, 59, 82]. Similarly, TILs with high CD103 expression within tumor cells have been found

to exhibit enhanced Notch signaling, which is known to support the proliferation of lung T_{RM} cells and promote the expression of the *IFNG* gene [36, 81]. Another study observed elevated Hobit expression in tumor-specific lung T_{RM} cells [83]. Given that the T-bet transcription factor induces Hobit expression, which subsequently promotes the maintenance of T_{RM} cells and IFN-γ signaling [44, 84], it is reasonable to suggest that Hobit expression in tumor-specific lung T_{RM} cells contributes to their retention and antitumor inflammatory properties.

Protective roles of TRM cells in skin cancer

Skin cancer is usually categorized into two major types: non-melanoma and melanoma. While non-melanoma skin cancer is the most prevalent, melanoma accounts for the majority of skin cancer-related deaths [85–87]. Similar to lung tumor-infiltrating T_{RM} cells, several studies have shown that $CD103^+$ T_{RM} cells in skin cancer exhibit high expression levels of CD39, PD-1, LAG-3, and CTLA-4 [50, 88]. In a mouse model study, $CD8^+$ T_{RM} cells amplified antitumor immunity by triggering antigen spreading through dendritic cells (DCs). The antigen-specific activation of T_{RM} cells leads to the maturation of cross-presenting dermal DCs and their migration to draining lymph nodes. This process enhances the cytotoxic $CD8^+$ T cell responses, contributing to tumor suppression, and has also been shown to improve survival in melanoma patients [75]. Another study demonstrated that $CD8^+$ T_{RM} cells in draining lymph nodes provide long-term immunity against metastatic melanoma, and their abundance is positively correlated with increased patient survival rates [89]. Notably, $CD8^+$ T_{RM} cells mediate melanoma suppression predominantly via TNF-α signaling, as their antitumor activity remains unaffected by deficiencies in IFN-γ or perforin [28].

Protective roles of TRM cells in brain cancer

Gliomas are the most common type of brain tumor, with glioblastoma being particularly notorious for its extremely poor prognosis and very low survival rate despite being a non-metastatic brain tumor [90, 91]. Similar to T_{RM} cells in other tissues, brain tumor-specific T_{RM} cells overexpress immune checkpoint receptors such as CD39, PD-1, CTLA-4, and Tim-3 [25, 92]. Multiple studies have suggested that $CD8^+$ T_{RM} cells provide effective anti-glioblastoma protection through TILs [93, 94]. Indeed, one study found that increased expressions of CD69 and CD103 are associated with a reduction in glioblastoma markers, including alpha-thalassemia/mental retardation, X-linked (ATRX), and tumor protein P53 (TP53) [93]. Additionally, the study showed that patients with high ITGAE (coding for integrin CD103) expression and high $CD8^+$ TIL abundance exhibited significantly enhanced survival rates, while low TIL abundance with high ITGAE expression was associated with reduced survival [93]. This study underscores the crucial role of $CD103^+$ T_{RM} cells in enhancing antitumor immunity and improving clinical outcomes in glioblastoma patients. Furthermore, reactivating virus-specific T_{RM} cells through intratumoral administration of virus-derived peptides was demonstrated to elicit local immune activation and provide notable antitumor effects, which enhanced survival in a murine glioblastoma model [95]. These findings suggest that tumor-specific T_{RM} cells and bystander T_{RM} cells, such as non-tumor-specific T_{RM} cells among TILs, can be utilized as an antitumoral therapeutic tool.

Protective roles of TRM cells in colorectal cancer

Colorectal cancer is classified into colon cancer (CC) and rectal cancer (RC) based on the location of tumor formation [96, 97]. Moreover, those two cancers are synonymously called colorectal cancer (CRC). T_{RM} cells in CRC are observed alongside the overexpression of immune checkpoint receptors such as CD39, PD-1, Tim-3, LAG-3, CTLA-4, and TIGIT, as well as the transcription factor Hobit, similar to tumor-infiltrating T_{RM} cells in other tissues [98, 99]. Several studies demonstrated that a high density of $CD8^+$ $CD103^+$ T_{RM} cells in colorectal tumor tissues is generally associated with a favorable prognosis [100, 101]. Additionally, Hobit was upregulated in CRC T_{RM} cells and correlated with an enhanced ability to infiltrate tumors, increased T cell receptor (TCR) responsiveness, and improved *IFNG*, *GZMB*, and *PRF1* gene expression and/or cytokine production [84, 102, 103]. Another study revealed that $CD8^+$ T_{RM} cells are more abundant in microsatellite instability-high (MSI-H) colorectal tumors compared to microsatellite-stable (MSS) tumors [104]; MSS tumors are characterized by normal DNA repair function and fewer mutations, making them less likely to be recognized by the immune system and less responsive to immunotherapy. In contrast, MSI-H tumors, with a higher mutation burden, tend to have better prognosis and respond more favorably to immune checkpoint inhibitors [105]. Notably, the higher presence of $CD8^+$ T_{RM} cells in MSI-H tumors suggests a potentially crucial role in immunogenicity, contributing to the ability of the immune system to control cancer growth and progression [104].

Protective roles of TRM cells in other cancers

T_{RM} cells are present in various NLTs, including the liver, kidney, and reproductive organs; however, their roles in cancer immunology remain less extensively characterized. Emerging evidence suggests that T_{RM} cells in these tissues contribute to immune surveillance and tumor regulation.

Recent studies have demonstrated that a poly (lactic-co-glycolic acid) (PLGA)-based nano/microparticle vaccine can activate non-tumor-specific $CD8^+$ T_{RM} cells in the liver, enhancing immune responses against hepatocellular carcinoma (HCC) and significantly improving survival rates in murine HCC models when combined with anti-PD-1 therapy [106]. Furthermore, HBV-specific T_{RM} cells have been associated with improved relapse-free survival in HCC, maintaining an antitumor immune response in a non-terminally exhausted state [107]. High infiltration of $CD103^+$ $CD8^+$ T_{RM} cells in CRC tissues is associated with a reduced incidence of liver metastasis, likely mediated by enhanced antitumor immunity, improved normalization of tumor vasculature, and synergistic interactions with anti-angiogenic therapies [100]. In renal cell carcinoma (RCC), a positive correlation has been observed between the number of $CD103^+$ cells, including T_{RM} cells, and prolonged survival in RCC patients [108]. $CD103^+$ T cells in RCC express high levels of PD-1, a major target of checkpoint inhibitors. Therefore, RCC-infiltrating $CD103^+$ T_{RM} cells are considered a potential therapeutic target for cancer treatment [109]. Similarly, ovarian cancer studies have shown that progenitor T_{RM} cells exhibit stem-like properties, replenishing effector T_{RM} cells as they undergo exhaustion. In addition, studies have reported that high densities of $CD103^+$ T_{RM} cells correlate with improved prognosis in ovarian cancer [110, 111].

Unfavorable roles of TRM cells in cancer

Although recent studies suggest that T_{RM} cells in tumors contribute beneficially to host protection, evidence indicates that, under certain circumstances, T_{RM} cells may also facilitate the progression of certain diseases. For example, in a chronic lung inflammation model induced by repeated exposure to *Aspergillus fumigatus*, $CD4^+$ $CD103^{low}$ T_{RM} cells exacerbated fibrosis through the production of effector cytokines, such as IL-5, IL-13, and IL-17, whereas $CD103^{hi}$ regulatory T (T_{reg}) cells acted to suppress the pathogenic responses [112]. In a study on human skin, the $CD49a^+$ $CD8^+$ T_{RM} cells presented specialized cytotoxic functions and excelled at producing IFN-γ. When stimulated using IL-15, the $CD49a^+$ $CD8^+$ T_{RM} cells rapidly upregulate cytotoxic effector molecules such as GZMB and perforin, enabling a potent cytotoxic response [20]. Furthermore, in a murine model study of Theiler's murine encephalomyelitis virus (TMEV) infection, $CD8^+$ antigen-specific T_{RM} cells persisted in the brain long after the virus was cleared. Upon reactivation, these T_{RM} cells triggered significant neuropathological responses characterized by systemic lymphopenia and pronounced neuroinflammation [113]. In a mouse colitis model study, $CD4^+$ T_{RM} cells expressing Hobit and Blimp-1 promoted chronic inflammation [114]. Mice lacking these transcription factors had significantly less severe colitis, reduced recruitment of myeloid cells, and lower levels of proinflammatory cytokines, such as IFN-γ, IL-13, and IL-17A [114]. In addition to their potential role in promoting severe disease progression, T_{RM} cells may also exert detrimental effects within the TME, contributing to unfavorable outcomes in certain cancer types. Below, we summarize the current understanding of the adverse roles of T_{RM} cells in tumors across various tissues (Fig. 2).

Unfavorable roles of TRM cells in lung cancer

Several studies have shown that the quantity of T_{RM} cells correlates with a better prognosis in lung cancer patients [81, 115]. However, one study suggests that while there is a high density of $CD8^+CD103^+$ T_{RM} cells, their presence or spatial organization may not be effective in controlling tumor growth, or it could contribute to an immunosuppressive environment [51]. While the exact reasons are not fully detailed, this may be due to the secretion of immunosuppressive cytokines or interactions with other immune cells that dampen the overall immune response against the tumor. In another study, T_{RM} cells in the lungs, particularly in individuals with a smoking history, were pivotal in influencing tumor evolution by facilitating immune evasion [116]. This finding has important implications for treating NSCLCs, as tumors in T_{RM} cell-enriched microenvironments may exhibit reduced responsiveness to current immunotherapeutic strategies [116]. Furthermore, studies have shown that tumor-infiltrating $CD103^+$ T_{reg} cells are associated with a poor prognosis in lung cancer patients due to their immunoregulatory functions, particularly dysregulating the expansion and cytotoxic functions of TILs [117, 118]. While the positive aspects of tumor-specific T_{RM} cells have been emphasized, their potential negative roles remain poorly studied and warrant further investigation.

Unfavorable roles of TRM cells in skin cancer

Numerous studies illustrate that the frequency of T_{RM} cells expressing certain markers positively correlates with skin cancer incidence [50, 119]. Indeed, $CD8^+$ $CD103^+$ T_{RM} cells in cutaneous squamous cell carcinoma (cSCC) are associated with a reduced time to cSCC metastasis [88]. This phenomenon may be attributed to the elevated expression of inhibitory molecules, such as PD-1, CTLA-4, and CD39, by $CD103^+$ T_{RM} cells in cSCC, suppressing their cytotoxic activity against tumor cells. In addition, these cells secrete the immunosuppressive cytokine IL-10, thereby exacerbating the suppression of the immune response. This immunosuppressive microenvironment impairs the antitumor functions of T_{RM} cells, facilitating

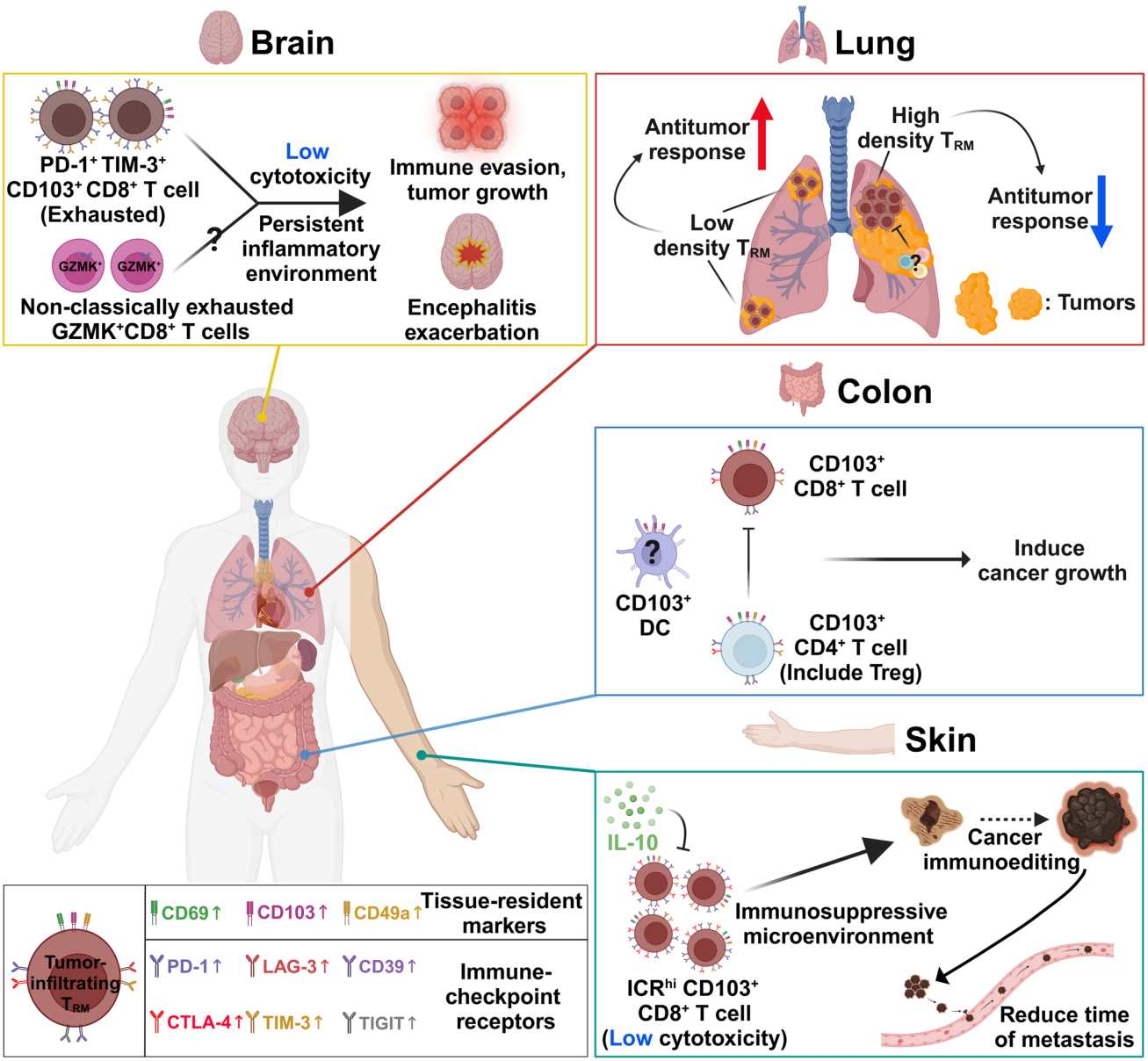

Fig. 2 Contribution of $CD103^+$ tissue-resident memory T (T_{RM}) cells across different tissues, highlighting their unfavorable roles in tumor progression and immune response in the brain, lung, colon, and skin. In the brain, exhausted programmed cell death protein 1 $(PD\text{-}1)^+$ T cell immunoglobulin and mucin domain 3 $(TIM\text{-}3)^+$ $CD103^+$ $CD8^+$ T cells, as well as potentially non-classically exhausted granzyme K $(GZMK)^+$ $CD8^+$ T cells may contribute to a low cytotoxic environment, promoting a persistent inflammatory state. This environment facilitates immune evasion and tumor growth, as well as exacerbating encephalitis. In the lungs, a high density of T_{RM} cells in the tumor microenvironment (TME) may contribute to the recruitment of immune-suppressive cells, creating an immune-suppressive environment that further inhibits T_{RM} cell functions and reduces antitumor responses. In the TME of the colon, $CD103^+$ $CD8^+$ T cells and particularly regulatory T cells among the $CD103^+$ $CD4^+$ T cells, along with $CD103^+$ dendritic cells (DCs) that may or may not induce cancer growth, potentially play important roles in promoting tumor progression. In the skin, immune checkpoint receptors $(ICRs)^{hi}$ $CD103^+$ $CD8^+$ T cells exhibit low cytotoxicity, and IL-10 additionally contributes to an immunosuppressive microenvironment, promoting cancer immune editing and accelerating metastasis

immune evasion and promoting rapid tumor metastasis. Furthermore, intraperitoneal administration of an anti-CD103 antibody in a mouse melanoma model reduced $CD8^+$ $CD103^+$ T cell levels and was associated with decreased tumor growth [120]. However, the involvement of $CD4^+$ $CD103^+$ T_{reg} cells in mediating these effects cannot be entirely excluded and warrants further investigation. Notably, CD103 is also expressed by T_{reg} cells, and previous studies have shown that depletion of T_{reg} cells can elicit antitumor responses in melanoma [120,

121]. Therefore, further research is needed to improve understanding of the role of tumor-specific T_{RM} cells with an unfavorable antitumor function.

Unfavorable roles of TRM cells in brain cancer

Similar to T_{RM} cells in other tissues, brain T_{RM} cells are recognized as important contributors to the antitumor response [93, 122, 123]. However, several studies have shown that higher PD-1 and/or TIM-3 expression in $CD8^+$ $CD103^+$ T cells correlates with poor prognosis in human glioblastoma patients [94, 124]. The mechanism through which this correlation may occur involves the association between PD-1 expression by T_{RM} cells and persistent neuroinflammation in conditions such as encephalitis [124]. Simply, immune-exhausted T_{RM} cells, characterized by high expression of inhibitory receptors such as PD-1 and TIM-3, may remain dysfunctional, leading to chronic neuroinflammation without mounting an effective cytotoxic response against tumor cells. This persistent inflammatory environment could fail to suppress tumor progression and may facilitate tumor growth by promoting immune evasion and tissue damage, ultimately exacerbating the disease [57, 125]. One study revealed that glioblastoma (GBM)-infiltrating $GZMK^+$ $CD8^+$ T cells do not express high levels of typical exhaustion markers such as TIGIT, LAG-3, and CTLA-4, nor do they exhibit significant cytotoxic markers such as GZMB, perforin, and IFN-γ [126]. These findings suggest that, while $GZMK^+$ T cells represent a clonally expanded effector population, unlike classically exhausted, they may still be functionally limited in their ability to eliminate tumor cells effectively. This could explain the limited efficacy of current immunotherapies in GBM [126]. Furthermore, one study demonstrated that high CD103 expression in glioma patients was associated with reduced survival [120]. However, this study did not specifically distinguish between CD8 and CD4 T cells, suggesting that the observed effect could be due to Treg cells, similar to $CD103^+$ Treg cells in the skin tumor model.

Unfavorable roles of TRM cells in colon cancer

Several studies have shown that the quantity of $CD103^+$ cells is not associated with a better prognosis in colon cancer [127, 128]. One study demonstrated that treatment with an anti-CD103 antibody significantly reduced tumor growth in a mouse colorectal cancer model [120]. However, this inverse correlation may occur because various cell types within the $CD103^+$ population, including $CD4^+$ Tregs, $CD8^+$ T_{RM} cells, DCs, and others, can influence the antitumor response through complex interactions. One study also revealed that $CD4^+$ $CD103^+$ T cells, in contrast to $CD8^+$ $CD103^+$ T cells, are associated with poorer prognosis in digestive tract cancers, highlighting distinct roles of tissue-resident T cell subsets within the TME [129]. Additional studies have revealed that $CD103^+$ $CD4^+$ T cells are markedly enriched in tumor tissues, strongly associated with advanced tumor stages, and correlate with poor overall survival outcomes. These cells exhibit high expression of the immunosuppressive cytokine IL-10 and markers of tissue residency yet lack lymph node homing markers, indicating a likely immunosuppressive function within the TME [130]. Furthermore, a high infiltration of $CD103^+$ $CD4^+$ T cells within tumors is associated with diminished $CD8^+$ T cell function, suggesting that these cells may play a critical role in establishing an immune evasive TME [130]. These findings indicate that $CD103^+$ TILs, possibly T_{reg} cells, may diminish the antitumor response in cancers.

Unfavorable roles of TRM cells in other cancers

Beyond several cancers, T_{RM} cells have also been implicated in tumor progression across various other tissues. For instance, in non-alcoholic steatohepatitis (NASH)-associated HCC, $CD8^+$ $PD\text{-}1^+$ T_{RM} cells exhibit dysfunctional immune surveillance, promoting tissue damage and facilitating tumor progression [131]. Moreover, anti-PD-1 immunotherapy exacerbates this effect by further activating these dysfunctional T cells. Similarly, in RCC, studies indicate that PD-1 and CTLA-4 blockade alone may be insufficient, as RCC paradoxically displays high levels of $CD8^+$ T cell infiltration correlated with poor prognosis, potentially due to immune cell heterogeneity, metabolic dysfunction, and associations with specific genomic alterations [132]. Therefore, alternative immune checkpoint therapies, metabolic pathway modulators, and precision treatments targeting relevant genetic alterations are being explored for their potential to enhance antitumor immunity while overcoming immunotherapy resistance [132]. Despite these insights, further research is required to clarify the precise role of T_{RM} cells in tumor progression across different cancers.

Potential valuable applications of TRM cells in cancer immunotherapy

Despite the potential deleterious roles that T_{RM} cells may play in certain cancer models, they remain a crucial component of the body's anti-cancer immunity and are considered by some researchers to be promising targets in the development of novel cancer immunotherapies. One approach to harnessing T_{RM} cells in immunotherapy is developing cancer-specific T_{RM} cells via vaccination studies. Indeed, studies have demonstrated that intradermal or intranasal vaccinations established $CD8^+$ T_{RM} cells in

target tissues of mice, which provided robust protection against cutaneous melanoma and pulmonary metastases, respectively [133, 134]. Another study demonstrated that vaccination-induced T_{RM} cells in an orthotopic head and neck cancer model generated effective antitumor immune responses, even without circulating T cell recruitment [82]. Specifically, intranasal vaccination of a cancer vector targeting DCs resulted in the local induction of $CD103^+$ T_{RM} cells, which were crucial for tumor control [82]. Even when the recruitment of circulating T cells was blocked, tumor growth was still significantly inhibited, suggesting that the locally resident T_{RM} cells were sufficient to mediate a strong antitumor effect [82]. Furthermore, other research has indicated that site-specific heterologous prime-boost vaccination strategies, such as cervicovaginal administration, are more effective in eliciting localized immune responses, including the induction of T_{RM} cells within the genital tract, which are critical for controlling HPV-associated tumors [135]. This approach highlights the potential of targeting T_{RM} cells to enhance the efficacy of immunotherapy by providing durable, localized immune protection against recurrent or persistent tumors [135]. Moreover, recent studies demonstrate that neoantigen hydrogel vaccines combined with immune checkpoint blockade can activate $CD8^+$ $CD69^+$ T_{RM} cells in liver metastases, enhancing tumor regression and long-term immune memory [136]. Overall, these findings suggest that T_{RM} cells are valuable for not only enhancing antitumor immunity but also as indicators in assessing the effectiveness of immunotherapy.

In addition to using vaccines to induce T_{RM} cells directly, other strategies can enhance T_{RM} cell activity and survival, such as utilizing ICIs. Several studies have demonstrated that ICIs targeting receptors such as PD-1 and CTLA-4 enhance the T_{RM} cell antitumor activity by upregulating the T help type 1 (Th1)/cytotoxic T (Tc1) cytokine genes and increasing the secretion of IFN-γ and TNF-α across various tissue environments [99, 137, 138]. One study investigating HCC revealed that T_{RM} cells within the tumor microenvironment exhibit an exhausted phenotype; however, these cells retain functional responsiveness to anti-PD-1 therapy, which effectively restores their capacity to secrete IFN-γ and TNF-α [139]. The study further identified an inverse correlation between PD-1 expression and T-bet levels in T_{RM} cells, suggesting that modulation of this axis may serve as a potential strategy to enhance T_{RM} cell-mediated antitumor immunity.

As mentioned above, ICI therapy targeting T_{RM} has shown promising therapeutic efficacy; however, conflicting findings have emerged, necessitating further research to resolve these inconsistencies and optimize treatment strategies. Recent studies suggest that ionic imbalances (e.g. K^+, Na^{2+}, Ca^{2+}, Zn^{2+}) lead to excessive ion influx, hyperpolarization, mitochondrial depolarization, and reduced Bcl-2/Bax ratio, contributing to T_{RM} dysfunction and apoptosis, indicating that targeting ionic homeostasis may enhance T_{RM}-based immunotherapies in RCC [140]. Modulation of these ionic pathways could represent a novel approach to improving the persistence and efficacy of T_{RM}-enriched treatments, particularly in solid tumors. Furthermore, EXO1 has been identified as a key gene in lung-T_{RM} cells, functioning as both a diagnostic and prognostic biomarker for lung adenocarcinoma (LUAD) [141]. Notably, elevated EXO1 expression correlates with poor prognosis and a reduced response to anti-PD-1/PD-L1 immunotherapy, suggesting its potential utility as a predictive marker for immunotherapy efficacy. In addition, in HCC, a higher T_{RM}-to-exhausted T cell (Tex) ratio has been associated with improved prognosis and an enhanced response to anti-PD-1 therapy, further supporting the potential of T_{RM} as predictive biomarkers for immune checkpoint blockade efficacy [142]. These findings underscore the critical role of T_{RM} in cancer immunotherapy, highlighting the need for further research to elucidate their clinical applications, optimize therapeutic strategies, and mitigate potential adverse effects.

However, comparatively, emerging evidence suggests that ICIs can induce adverse effects, such as irAEs [143]. This is because immune checkpoint receptors are crucial in maintaining self-tolerance, preventing the immune system from attacking the body's cells and tissues [144]. Therefore, further research is needed to improve the balance between enhancing antitumor immunity and controlling irAEs.

Another approach to utilizing T_{RM} cells in cancer immunotherapy is chimeric antigen receptor (CAR) T cell therapy. However, due to several significant challenges, CAR T cell therapy has demonstrated limited efficacy in solid tumors. These include the difficulty in identifying tumor-specific antigens, the presence of an immunosuppressive TME, and the restricted infiltration of CAR T cells into the dense stromal architecture of solid tumors [145]. Furthermore, CAR T cells often exhibit reduced persistence within the TME and may induce off-tumor toxicity by targeting normal tissues that express similar antigens [145]. Collectively, these factors attenuate the therapeutic efficacy of CAR T cells in solid tumors.

However, one study has explored the use of tissue-resident memory CAR T cells, showing that exposure to TGF-β during CAR T cell production enhances their stem-like properties and tissue residency [146]. These reprogrammed CAR T_{RM} cells exhibit superior tumor infiltration, prolonged persistence, and improved control of solid and liquid tumors compared to conventional CAR T cells [146]. Additionally, these CAR T_{RM} cells resist tumor-imposed dysfunction and maintain robust antitumor activity, highlighting their potential as a more effective strategy for immunotherapy, particularly in solid tumors where traditional CAR T cell therapies have presented limited success. In conclusion, T_{RM} cells hold

significant potential in cancer immunotherapy, as direct targets for vaccine-based strategies, and as enhanced components in therapies such as CAR T cell treatment.

While challenges remain, particularly regarding immune-related adverse effects and tumor-specific targeting, harnessing the unique properties of T_{RM} cells could lead to more durable and localized antitumor responses, especially in solid tumors.

Conclusion

T_{RM} cells are extensively recognized for their robust protective role in NLTs against foreign antigens. Furthermore, T_{RM} cells have been shown to play crucial roles in antitumor immunity, contributing to improved survival rates and the suppression of tumor growth across various cancer types. However, recent studies have revealed that T_{RM} cells may exhibit paradoxical functions, potentially facilitating tumor progression in certain contexts and leading to adverse effects on antitumor immune responses. Notably, studies reporting the detrimental roles of T_{RM} cells often involve limited sample sizes, raising concerns about potential biases. However, an increasing number of recent studies have consistently reproduced these findings, strengthening their validity. Furthermore, research utilizing mouse models and mechanistic investigations has provided additional evidence supporting these observations, enhancing their credibility. And interestingly, some studies suggest that bystander or virus-specific T_{RM} activation may enhance cancer-protective effects, indicating that the role of T_{RM} cells as either protective or unfavorable can vary depending on the tumor types and microenvironment as well as presence or absence of underlying diseases in the host. Despite these negative aspects, T_{RM} cells can provide valuable insights into the immune system and hold significant potential for advancing immunotherapies against cancer development and progression. Thus, developing a deeper understanding of these complex T_{RM} cell functions is crucial to fully harnessing their therapeutic potential in cancer immunotherapy. Therefore, this review aimed to comprehensively examine the dual roles of T_{RM} cells within different tumor environments, highlighting both their protective effects against cancer and their potential to exacerbate tumor growth. Additionally, we discussed the implications of T_{RM} cell behaviors for future cancer therapies, underscoring the importance of further research to optimize the therapeutic use of T_{RM} cells while minimizing their harmful effects.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare that there are no potential conflicts of interest.

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