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REVIEW

Immune Memory Focus

Tissue-resident memory T cells in tumor immunity and immunotherapy

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Tissue-resident memory T cells (T_{RM}) represent a heterogeneous T cell population with the functionality of both effector and memory T cells. T_{RM} express residence gene signatures. This feature allows them to traffic to, reside in, and potentially patrol peripheral tissues, thereby enforcing an efficient long-term immune-protective role. Recent studies have revealed T_{RM} involvement in tumor immune responses. T_{RM} tumor infiltration correlates with enhanced response to current immunotherapy and is often associated with favorable clinical outcome in patients with cancer. Thus, targeting T_{RM} may lead to enhanced cancer immunotherapy efficacy. Here, we review and discuss recent advances on the nature of T_{RM} in the context of tumor immunity and immunotherapy.

Introduction

Tissue-resident memory T cells (T_{RM}) reside in peripheral tissues, patrol their surroundings, and rapidly respond to alarming signals (Jiang et al., 2012; Schenkel et al., 2014; Park and Kupper, 2015; Clark, 2015; Dijkgraaf et al., 2019). These features enable them to potentially serve as critical players in antitumor surveillance and immunity. Early studies in viral infections have revealed that T cells were retained in tissues, including human and murine skin as well as murine small intestine and lung tissues (Zhu et al., 2007; Gebhardt et al., 2009; Masopust et al., 2010; Teijaro et al., 2011). In support of T_{RM} tissue retention, T_{RM} down-regulate the expression of markers for tissue egress and express surface molecules that enable their retention in tissues (Kumar et al., 2017; Park et al., 2019; Raphael et al., 2020; Byrne et al., 2020). T_{RM} differentiation is guided by transcription programs common to both effector and memory T cells (Milner and Goldrath 2018), consistent with their persistence in tissues as memory T cells yet retaining rapid effector function for immune protection. T_{RM} are defined in multiple infection models to be retained in tissues, as shown in parabiosis experiments in mice, antibody in vivo labeling, and in other approaches that mark and monitor tissue T cells (Szabo et al., 2019; Masopust and Soerens, 2019). Of note, the transcriptome signature of T_{RM} suggests a "tissue-tailored" retention model rather than a "one size fits all" model, highlighting tissue- and organ-specific immune regulation, also named tissue- and organ-specific "immunostats" (Amsen et al., 2018; Pao et al., 2018). Tissue-specific adaptations may enable T_{RM} to maintain homeostasis in a site-specific fashion. Intriguingly, transcriptionally and functionally distinct T_{RM} subsets and T_{RM} precursors have been observed in the murine small intestine during infection (Kurd et al., 2020). This suggests a high heterogeneity and complexity of T_{RM} populations.

Compared with their protective role in infectious diseases (Wu et al., 2018; Wilk and Mills, 2018; Muruganandah et al., 2018; O'Hara et al., 2020), the importance and significance of T_{RM} in tumor immunity are not adequately characterized. Nevertheless, recent studies in cancer-bearing mouse models have indicated a pivotal role of T_{RM} in antitumor immunity in several tumor types (Nizard et al., 2017; Milner et al., 2017; Malik et al., 2017; Enamorado et al., 2017). Moreover, human studies show an association between tumor T_{RM} and improved responses to immunotherapy and favorable clinical outcome in patients with cancer (Table 1). These findings fuel interest in T_{RM} research in cancer immunology and immunotherapy. Here, we review the current understanding of T_{RM} from mouse

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Table 1. **Clinical relevance of T_{RM} in patients with cancer**

Cancer types	T_{RM} phenotype	Correlation with clinical features	References
Breast cancer	$CD8^+$, $CD103^+$	Intratumoral $CD103^+CD8^+$ T cells are positively associated with RFS and OS in estrogen receptor–negative basal-like breast cancer.	Wang et al., 2016
		$CD8^+$ T_{RM} gene signature is associated with improved DFS and OS in patients with TNBC.	Savas et al., 2018
		Levels of $CD103^+CD8^+$ T cells are higher in TNBCs in patients without tumor relapse than with tumor relapse.	Egelston et al., 2019
Bladder cancer	$CD8^+$, $CD103^+$, $CD69^+$, $CD49a^+$, $PD\text{-}1^+$	Levels of $CD103^+CD8^+$ T cells are negatively associated with tumor size and are positively associated with OS and RFS.	Wang et al., 2015
		High T_{RM} tumor infiltration is associated with lower tumor stage.	Hartana et al., 2018
Cervical cancer	$CD8^+$, $CD103^+$, $PD\text{-}1^+$, $GzmB^+$	CD103 expression is associated with improved DSS.	Komdeur et al., 2017
		Prognostic benefit of increased CD103 expression is observed in patients treated with radiotherapy.	
		Abundance of intraepithelial $CD103^+$ cells is associated with improved DSS and DFS in patients with or without radio(chemo) therapy.	
Colorectal cancer	$CD8^+$, $CD103^+$	High density of $CD103^+$ cells is associated with DFS.	Huang et al., 2017
		High density of $CD103^+$ cells is negatively associated with OS and DFS in patients with *KRAS* WT tumors.	
Endometrial cancer	$CD8^+$, $CD103^+$, $PD\text{-}1^+$	$CD103^+$ cells are associated with prolonged DSS.	Workel et al., 2016
Esophageal cancer	$CD8^+$, $CD103^+$, $PD\text{-}1^+$, $TIM3^+$	High density of $CD103^{hi}CD8^{hi}$ cells is associated with improved OS.	Han et al., 2020
Gastric cancer	$CD103^+$, $CD69^+$, $PD\text{-}1^+$, $TIGIT^+$, $CD39^+$	Presence of $CD8^+CD103^+$ cells is associated with improved OS.	Lin et al., 2020
Hepatocellular carcinoma	$CD8^+$, $CD103^+$	High density of $CD8^+CD103^+$ cells is associated with improved OS.	Lim et al., 2019
Head and neck cancer	$CD8^+$, $CD103^+$, $CD39^+$	High frequencies of $CD103^+CD39^+$ cells are associated with improved OS.	Duhen et al., 2018
		High expression of CD103 is associated with improved OS.	
Lung cancer	$CD8^+$, $CD103^+$ $CD69^+$, $CD49a^+$, $PD\text{-}1^+$, $4\text{-}1BB^+$, $CXCR6^+$ $CD39^+$, $TIM3^+$	High levels of $CD103^+$ cells are associated with improved OS in total tumor and stromal region.	Djenidi et al., 2015
		High levels of $CD103^+$ cells are associated with improved DFS in total tumor, epithelial tumor islets, and stromal region.	Ganesan et al., 2017
		High density of $CD103^+$ cells is associated with improved OS.	Duhen et al., 2018
		High expression of both CD103 and CD39, as well as CD103 alone, is associated with improved OS.	Koh et al., 2017
		High numbers of intratumoral, but not stromal, $CD103^+$ cells are associated with prolonged DFS and OS.	Clarke et al., 2019
		$PD\text{-}1^+TIM3^+$ cells are enriched in responders to anti–PD-1 therapy.	Nizard et al., 2017
		High intratumoral $CD103^+$ cells are associated with improved OS.	
Melanoma	$CD8^+$, $CD103^+$, $CD69^+$, $CD49a^+$, $PD\text{-}1^+$, $LAG\text{-}3^+$, $GzmB^+$	High levels of CD49a expression are associated with improved DFS and OS.	Murray et al., 2016; Edwards et al., 2018; Menares et al., 2019
		Increased numbers of $CD69^+CD103^+CD8^+$ cells are associated with improved OS in immunotherapy-naive patients.	
		Enrichment of T_{RM} gene signature is associated with improved OS.	
Ovarian cancer	$CD8^+$, $CD103^+$, $PD\text{-}1^+$, $CD3^+$	Presence of $CD103^+$ cells is associated with increased DSS in HGSOC and mucinous cancers.	Webb et al., 2014
		Patients with HGSOC, containing both $CD103^+$ and $PD\text{-}1^+$ cells, are associated with increased DSS.	Webb et al., 2015

Table 1. **Clinical relevance of T_{RM} in patients with cancer (*Continued*)**

Cancer types	T_{RM} phenotype	Correlation with clinical features	References
		$CD103^+$ cell numbers are associated with improved DSS in patients treated with PS.	Bösmüller et al., 2016
		High infiltration of $CD103^+$ cells in tumor parenchyma of primary tumors is associated with improved 10-yr OS.	Komdeur et al., 2016
			Santoiemma et al., 2016
Pancreatic cancer	$CD8^+$, $CD103^+$	Increased ratio of $CD8^+CD103^+$ cells to $CD8^+CD103^-$ cells is associated with improved DFS.	Lohneis et al., 2017

DFS, disease-free survival; DSS, disease-specific survival; HGSOC, high-grade serous ovarian cancer; OS, overall survival; PS, primary surgery and adjuvant chemotherapy; RFS, relapse-free survival; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domains; TNBC, triple-negative breast cancer.

infection models and human studies and how these findings have been used to guide studies of T_{RM} in tumor immunity, as well as implications for the role of T_{RM} in immune surveillance and immunotherapies.

Identifying T_{RM}

T_{RM} are defined based on the expression of specific markers, a distinct transcriptional profile, and their functional retention in tissues, all properties that distinguish T_{RM} from circulating memory T cells, including effector memory T cells (T_{EM}) and central memory T cells (T_{CM}). Based on this definition, $CD8^+$ T_{RM} are found to be a component of tumor-infiltrating lymphocytes (TILs) in patients with solid tumors (Byrne et al., 2020). However, it is important to note that T_{RM} are loosely defined in different studies in the context of tumor immunity.

T_{RM} express tissue retention markers, including CD69 (C-type lectin), αE(CD103)β7 (E-cadherin receptor), and α1(CD49a)β1 (VLA-1), and exhibit reduced expression of migration and tissue egress markers, such as CCR7, CD62L, and sphingosine-1-phosphate receptor 1 (S1PR1; Schenkel and Masopust, 2014; Kumar et al., 2017; Szabo et al., 2019). Other core markers identified in both human and mouse T_{RM} include the chemokine receptor CXCR6, the inhibitory receptor programmed death receptor 1 (PD-1), and CD101, which have inhibitory function (Mackay et al., 2016; Kumar et al., 2017; Wein et al., 2019). The expression of T_{RM}-associated markers differs between organs and tissue sites. CD103 is most highly expressed by $CD8^+$ T_{RM} in mucosal and barrier sites, is variably expressed by T_{RM} in lung and skin, and is not expressed by T_{RM} in lymphoid sites (Kumar et al., 2017; Steinert et al., 2015). PD-1 is highly expressed by human T_{RM} in exocrine sites, such as the pancreas, and to a lesser extent by lymphoid T_{RM}, but is not highly expressed by intestinal T_{RM} (Weisberg et al., 2019). In human tumors, T_{RM} phenotype can also vary according to the tumor type (Table 1). Interestingly, human T_{RM} associated with multiple tumor types in different sites express CD103, possibly due to the epithelial origin of many solid tumors, while lung tumor–associated T_{RM} also express CXCR6 mRNA (Ganesan et al., 2017). PD-1 is expressed by T_{RM} in tumor tissues and healthy tissues. Tumor-associated myeloid APCs, including macrophages and myeloid dendritic cells (DCs), highly express programmed death-ligand 1 (PD-L1; B7-H1), engage $PD\text{-}1^+$ T cells, and mediate immune suppression in spontaneous and immunotherapy-induced tumor immunity (Curiel et al., 2004; Zou et al., 2016; Lin et al., 2018). It is unknown if $PD\text{-}L1^+$ APCs interact with $PD\text{-}1^+$ T_{RM}, resulting in T_{RM} functional alteration in the tumor-draining LNs and tumor microenvironment. Additionally, whether tumor-associated T_{RM} in a particular tissue site differ phenotypically from T_{RM} in the identical healthy tissue site requires further investigation.

Transcriptome profiling of the population and single-cell RNA sequencing (scRNAseq) have elucidated core features of T_{RM} in mouse models and humans and further revealed T_{RM} heterogeneity and tissue-specific signatures. Population-level RNAseq of mouse and human T_{RM} has revealed conserved signatures that include genes encoding the surface and intracellular molecules described above, as well as transcriptional regulators (Mackay et al., 2016; Kumar et al., 2016; Hombrink et al., 2016). In mice, the transcription factors (such as Hobit, Blimp-1, Runx3, and Id2 family members) have been reported to play a role in T_{RM} biology (Mackay et al., 2016; Milner et al., 2017; Milner et al., 2020). Human T_{RM} do not express elevated levels of Hobit, although Notch expression is up-regulated and is related to T_{RM} establishment (Hombrink et al., 2016; Kumar et al., 2017). A "master regulator" defining human T_{RM} development has not yet been identified. However, single-cell transcriptome profiling of T_{RM} has begun to reveal new insights into distinguished features of T_{RM}, including their heterogeneity and tissue-specific variations. In humans, scRNAseq analysis of T cells from lung and lymphoid sites has revealed a T_{RM}-associated tissue gene signature, including cell–cell communication, cell structure, and cell–cell matrix interactions (Szabo et al., 2019). This suggests that cell structure and cell interaction may regulate T_{RM} formation and maintenance. Transcriptome analysis has also indicated considerable heterogeneity among mouse T_{RM} populations (Milner et al., 2020).

Transcriptome analysis has likewise identified tumor-associated T_{RM} subsets in the tumor microenvironment. For example, single-cell sequencing suggests different T_{RM} subsets in human breast cancer (Savas et al., 2018). Interestingly, PD-1–expressing T_{RM} may possess superior functionality when compared with PD-1–expressing non-T_{RM}, as suggested in transcriptome profiling of human lung cancer (Clarke et al., 2019). Based on our current understanding of PD-L1 and PD-1 in

tumor immunity (Curiel et al., 2004; Zou et al., 2016; Lin et al., 2018), this finding is unexpected. Transcriptionally distinct subsets of T_{RM}, including Blimp1^{hi} and Id3^{hi} subpopulations, were also identified in a mouse melanoma model (Fig. 1; Milner et al., 2020). Although transcriptome studies have generated some insight into T_{RM} in tumors, it is important and critical to phenotypically and functionally define the different subsets of tumor-associated T_{RM}, including PD-1$^+$ T_{RM}. Notably, although tumor-infiltrating lymphocytes show a T_{RM}-like signature, there are no specific phenotypic and functional markers to define T_{RM} among different memory T cell subsets in the tumor microenvironment (Sasson et al., 2020). Thus, functional studies following single-cell phenotyping are critical to resolve discrepancies regarding different tumor-infiltrating T cell subsets, including T_{RM}.

T_{RM} retention

T_{RM} were originally identified in mice using parabiosis models and in vivo antibody labeling (Anderson et al., 2014; Szabo et al., 2019). Multiple molecules (including CD44, CD69, integrins [CD49a, CD103]), some transcription factors (i.e., Notch, Runx3, Blimp1, Hobit), fatty acid–binding proteins (FABPs), and microbiome-derived metabolites (such as short-chain fatty acid [SCFA]) are reported to be involved in T_{RM} retention in the tissue. CD44 is a receptor for extracellular matrix and assists T_{RM} interaction with epithelial cells and collagen (Amsen et al., 2018). CD69 restrains the function of S1PR1 signaling and blocks T_{RM} egress from tissue (Skon et al., 2013; Mackay et al., 2015). Similarly, CD49a and CD103 function as "anchors" to arrest T_{RM} within the tissues (Chen and Shen, 2020; Byrne et al., 2020).

The pathways controlling T_{RM} retention in tumors are poorly defined. Different levels of CD8$^+$CD103$^+$ T_{RM} are found in tumor epithelium and tumor stroma in different tumor types in patients (Cresswell et al., 2001; Ling et al., 2007; Djenidi et al., 2015; Wang et al., 2015; Workel et al., 2016; Nizard et al., 2017), suggesting that CD103 may be particularly important for T_{RM} retention in tumors. Antibody blockade of CD103 or genetic deficiency of CD103 results in reduced tumor-infiltrating T cells and accelerated tumor progression in mice (Sandoval et al., 2013; Murray et al., 2016; Sun et al., 2016; Malik et al., 2017), supporting a role for CD103 in T cell tumor retention. Notch plays a role in controlling maximal CD103 expression in tumor-associated T_{RM} (Hombrink et al., 2016). Transcription factors, including Runx3, Blimp, Hobit, and KLF2, have been shown to down-regulate homing receptor expression for egress in T_{RM} and promote T_{RM} tissue retention in mouse infection models (Milner et al., 2017; Mackay et al., 2016; Skon et al., 2013). The potential role of these transcription factors in T_{RM} tumor retention remains to be established.

It appears that T_{RM} retention is subject to their adaptation to and regulation by their tissue of residency. Consistent with this concept, tissue-tailored, variable, and malleable profiles of FABP isoforms are found in murine T_{RM} after viral infection (Frizzell et al., 2020). Interestingly, microbiota-derived SCFA favors CD8$^+$ T cell long-term survival and memory (Bachem et al., 2019). Altogether, these early studies suggest that it is crucial to decode molecular mechanisms by which T_{RM} gain tissue-tailored "labels" and to characterize the "area code" to control T_{RM} memory, survival, and function in the tumor microenvironment in different tumor types.

Generation and maintenance of T_{RM}

Several models (including linear, asymmetrical, self-renewal, simultaneous, "one cell, one fate," and "one cell, multiple fates" programs) are proposed to explain T_{RM} differentiation (Enamorado et al., 2018; Raphael et al., 2020). Moreover, T_{RM} differentiation is influenced by different factors at the earliest priming stage in the LN, the cytokine environment during differentiation and activation, and finally through tissue-specific influences. At the level of priming, murine Batf3-dependent DCs and human CD1c$^+$/CD163$^+$ TGF-β–producing DCs can prime T cells for T_{RM} generation in lymphoid tissues (Mami-Chouaib et al., 2018; Amsen et al., 2018; Bourdely et al., 2020). DC-specific DNGR-1 (CLEC9A) provides optimal signal for murine T_{RM} generation (Iborra et al., 2016). Even before antigen encounter, naive T cells can undergo "training" in the LNs via interacting with migratory αVβ8$^+$ DCs. These DCs activate and present TGF-β to naive CD8$^+$ T cells, resulting in T_{RM}-like features, including up-regulation of CD103 expression and epigenetic modifications of T_{RM}-related genes (Mani et al., 2019). It is speculated that DCs in the tumor-draining LNs may similarly affect T_{RM} development in the tumor microenvironment.

T_{RM} undergo a unique, hybrid effector cell–memory cell differentiation program driven by transcription factors associated with both memory and effector cell characteristics. For example, Blimp1 and Notch are required for T_{RM} and favor T_{EM}, whereas Runx3 and Nr4a1 promote T_{RM} and support T_{CM} (Milner and Goldrath, 2018). Conversely, T-bet and Eomes inhibit T_{RM} formation but promote T_{EM} and T_{CM} differentiation, respectively. Furthermore, T_{RM} seem to be reminiscent effector cells via expression of PD-1, IFNγ, perforin, and granzyme B (GzmB) on both mRNA and protein levels (Szabo et al., 2019; Milner and Goldrath, 2018; Ganesan et al., 2017), and they share properties of stem cells, as they may be long-lived and not terminally differentiated (Milner and Goldrath, 2018). Overall, coexistence of these memory-, effector-, and stem-like properties may reinforce the antitumor functionality of T_{RM}.

Cytokines at the tissue site or during priming can influence T_{RM} formation

Notably, TGF-β promotes CD103 expression and is critical for formation of T_{RM} in the gut, skin, and lungs (Zhang and Bevan, 2013; Raphael et al., 2020). TGF-β can be highly expressed in the tumor microenvironment and may promote T_{RM} establishment. Tissue-specific factors are also important for T_{RM} establishment at specific sites. The cutaneous lymphocyte antigen and chemokine receptors, including CCR4, CCR8, CCR10, and CCR19, are expressed on T_{RM} resident in the skin, whereas CCR9, CXCR3, and integrin $\alpha_4\beta_7$ are revealed in intestinal-resident T_{RM} (Farber et al., 2014; Amsen et al., 2018; Sun et al., 2019). Murine T_{RM} in the kidney have enhanced expression of E-selectin and P-selectin (Ma et al., 2017). CXCR6 controls T_{RM} trafficking to murine lungs (Wein et al., 2019) and is expressed in T_{RM} in human lung cancer (Ganesan et al., 2017), while murine T_{RM}

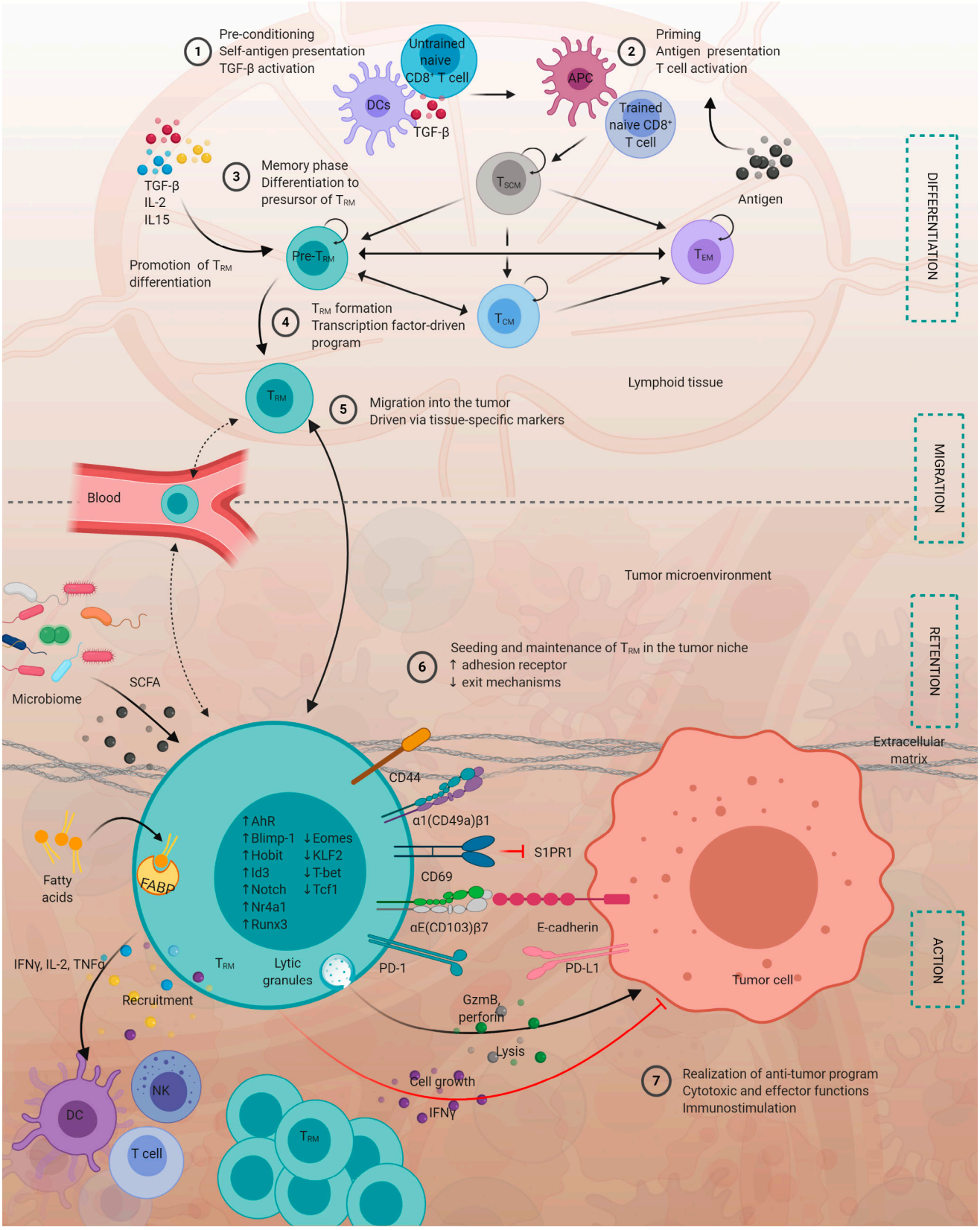

Figure 1. **T_{RM} in tumor immunity.** (1 and 2) Before specific antigen priming, $CD8^+$ naive T cells may interact with DCs in the presence of TGF-β. This process may prepare T_{RM} formation. (3) During memory phase, T_{SCM} may give rise to different memory subsets, including T_{RM}. IL-2, IL-15, and TGF-β, which may provide optimal signaling for T_{RM} formation. (4) T_{RM} precursors may undergo a transcription factor–driven generation program. (5) T_{RM} can traffic into the tumor microenvironment, and they are maintained in situ without (or with minimal) recirculation. (6) T_{RM} retention in tumors may be related to certain

integrins, including CD44, α1(CD49a)β1, αE(CD103)β7, and CD69. CD44 and α1(CD49a)β1 tether T_{RM} to the extracellular matrix. αE(CD103)β7 anchors T_{RM} via interacting with E-cadherin on the epithelial cell surface. CD69 blocks S1PR1-mediated "exit" signaling. Blockade of T_{RM} egress from the tissue may be promoted by up-regulation of some transcription factors (including Blimp, Hobit, Notch, and Runx) and by down-regulation of Krüppel-like factor 2 (KLF2). Microbiome-derived SCFA may promote long-term maintenance of T_{RM}. FABP and FFA uptake may favor T_{RM} survival and antitumor functionality. T_{RM} may express immune checkpoint proteins, suggesting that T_{RM} likely responds to checkpoint blockade. (7) T_{RM} may release perforin and GzmB and directly kill target tumor cells. T_{RM}-derived cytokines (IFN-γ, IL-2, and TNF-α) promote infiltration of DCs, T and B cells, and natural killer cells, indirectly boosting antitumor immunity.

migrate to the brain via CCR5 and CXCL10 (Glass et al., 2005; Klein et al., 2005). However, $\alpha_4\beta_7^+$ T_{RM} are also present in the murine skin (Ohmatsu et al., 2010). CXCR3 can "navigate" T_{RM} to the lungs, skin, and vagina, whereas P-selectin plays a role in migration of $CD4^+$ T_{RM} to the intestine (Haddad et al., 2003; Jeyanathan et al., 2017; Chen and Shen, 2020). Future studies are required to precisely characterize T_{RM}-related functional states in different tumors.

Once established in the tissues, there is evidence that T_{RM} can be maintained for a long period of time. Mouse studies in a parabiosis model show that $CD4^+$ and $CD8^+$ T_{RM} generated from site-specific infection do not emerge into the circulation and enter peripheral organs during homeostasis for several weeks (Teijaro et al., 2011; Jiang et al., 2012; Steinert et al., 2015). Additionally, T_{RM} are identified from intravenous antibody labeling due to their presence in tissues, not in the vasculature (Anderson et al., 2012; Turner et al., 2014). In humans, long-term persistence of $CD4^+$ and $CD8^+$ T_{RM} has been demonstrated in transplanted organs in which donor T_{RM} in lungs and intestines were maintained for over a year after transplant but were not detected in blood (Snyder et al., 2019; Bartolomé-Casado et al., 2019; Bartolomé-Casado et al., 2020; Pallett et al., 2020). Moreover, T_{RM} frequencies in multiple mucosal barriers and lymphoid sites are stably maintained throughout decades of adult life (Kumar et al., 2018). Together, these findings suggest that T_{RM} maintenance is tissue specific and integral for tissue homeostasis.

Studies in mice suggest that T_{RM} persistence and stability in tissues can be variable

Lung $CD8^+$ T_{RM} generated after infection tend to wane over time, unless persistent antigen stimulation is provided (Uddbäck et al., 2021). Over time, lung T_{RM} were also found to migrate out of the lung to the associated lymphoid tissue (Stolley et al., 2020). Recent studies have found low levels of potential T_{RM} in healthy human peripheral blood (Klicznik et al., 2019; Guggino et al., 2019) and in the synovial fluid of individuals with spondyloarthritis (Guggino et al., 2019; Qaiyum et al., 2019). In line with this, scRNAseq analysis identifies a tissue gene signature in a minor fraction of peripheral blood T cells (Szabo et al., 2019). Thus, it seems that T_{RM} emergence into the circulation may occur, but it may be a rare event. In mice, reactivation of T_{RM} in secondary infection can result in migration of effector progeny to the local draining LNs (Fonseca et al., 2020; Stolley et al., 2020). Adoptive transfer of purified mouse T_{RM} can enable T_{RM} to migrate to and populate different tissue sites in response to systemic virus challenge (Fonseca et al., 2020). While these results suggest T_{RM} plasticity for reactivation, further studies are needed to investigate the trafficking and retention properties of T_{RM} in different sites; this is an important research area in T_{RM} biology.

Tumor-infiltrating T cells have been studied before the identification of T_{RM}

Tumor-associated T_{RM} may consist of T_{RM} already in the original tissue site before tumorigenesis and T cells that migrate from the periphery, which become T_{RM} due to certain tumor environmental factors such as TGF-β (Fig. 1). Based on results in murine infection models, we propose that tumor-specific T_{RM} reside primarily in the tumor milieu, where they may locally proliferate in response to antigen encounter in situ without or with minimal exiting from the tumor site. This concept is in agreement with the data that tumor-associated antigen-specific T cells are largely found in tumor tissue rather than in the circulation (Webb et al., 2014; Smazynski and Webb, 2018). Recall immune responses could be initiated at nonlymphoid tissues, such as tumor tissues (Zou, 2005). If so, tumor-infiltrating T_{RM} may be locally activated to proliferate and combat tumor cells in the tumor microenvironment. Subsequently, they may exit the primary tumor niche and inhabit new sites within the tissue of origin—for instance, metastatic tumor tissues. Given that the majority of cancer patients die from tumor metastases, boosting T_{RM}-mediated long-term local and systemic memory would be meaningful. Nonetheless, the potential mechanisms controlling tumor-associated T_{RM} maintenance, replenishment, and function remain to be dissected.

Role of T_{RM} in tumor immune surveillance and immunity

Due to their long-term retention in multiple tissues, T_{RM} can play an important role in both tumor immune surveillance and immunity at diverse sites, analogous to their role in immune protection to pathogens (Amsen et al., 2018; Gebhardt et al., 2018; Byrne et al., 2020). Recent studies in mice have pointed toward the functional importance of T_{RM} in immune responses (Park et al., 2018; Beura et al., 2018a; Klicznik et al., 2019; Fonseca et al., 2020). One intriguing possibility is that T_{RM} may eliminate transformed cells in situ, thereby preventing tumor initiation. However, once a tumor is established, tumor cells outcompete tumor-infiltrating T cells for nutrients, resulting in impaired T cell functionality (Zhang et al., 2017; Bian et al., 2020). Correspondingly, human gastric cancer cells outcompete T_{RM} for lipid uptake, resulting in T_{RM} death (Lin et al., 2020). The data suggest that fatty acids may be required for T_{RM} survival in the tumor niche.

T_{RM} mediate antitumor immunity directly through production of effector and cytolytic mediators and through the release of cytokines and chemokines for immune cell recruitment and activation. $CD8^+$ T_{RM} can be reactivated by both hematopoietic

and nonhematopoietic APCs within the sites, which can shape their functionality (Low et al., 2020). Once stimulated, T_{RM} release lytic granules containing perforin and GzmB and kill tumor cells, similarly to effector CD8$^+$ T cells (Amsen et al., 2018). Furthermore, T_{RM} can support immune equilibrium in a melanoma mouse model and contribute to tumor control (Park et al., 2019a).

Interestingly, tumor-infiltrating CD8$^+$CD39$^+$CD103$^+$ T_{RM} elicit more potent cytotoxic and effector functions compared with CD103$^-$ counterparts (Franciszkiewicz et al., 2013; Djenidi et al., 2015; Enamorado et al., 2017; Malik et al., 2017; Nizard et al., 2017; Duhen et al., 2018; Park et al., 2019; Sasson et al., 2020). In line with this, CD8$^+$CD103$^+$ T_{RM} in tumor, but not in tumor stroma, are a better prognostic factor in patients with cancer (Koh et al., 2017; Dhodapkar, 2018). Human tumor-infiltrating T helper type 17 (Th17) cells are affected by TGFβ in the tumor microenvironment, express CD49, are long-lived memory cells, and mediate potent antitumor immunity (Kryczek et al., 2009; Kryczek et al., 2011). These features suggest that human tumor-infiltrating Th17 cells exhibit and/or gain a T_{RM} phenotype. Correspondingly, CD4$^+$ T_{RM} with a Th17 signature have been observed in patients with autoimmune disease (Krebs et al., 2020). Interestingly, CD49a$^+$ T_{RM} are the most effective tumor killers among T cells in a melanoma mouse model (Le Floc'h et al., 2007; Djenidi et al., 2015; Murray et al., 2016). It is tempting to speculate that T_{RM} may possess superior antitumor activity compared with other tumor-associated lymphocytes.

In addition to tumor killing via their direct cytotoxic activity, T_{RM} function as an immune stimulator. T_{RM}-derived effector cytokines stimulate local DCs, natural killer cells, and T cells to boost antitumor immune responses (Schenkel et al., 2013; McMaster et al., 2015; Hombrink et al., 2016; Glasner et al., 2018). Furthermore, T_{RM} more rapidly respond to antigen re-exposure compared with circulating memory T cells (Mackay et al., 2012; Schenkel et al., 2014; Ariotti et al., 2014). Therefore, T_{RM} may play a crucial role against tumor recurrence. Collectively, activated T_{RM} initiate a system of a rapid, tissue-wide state of alarm for optimal immune protection. Unexpectedly, although T_{RM} express inhibitory checkpoint receptors, their cytotoxic and effector functionalities are maintained (Ganesan et al., 2017; Savas et al., 2018; Boddupalli et al., 2016). Treatment with PD-1 and PD-L1 blockade results in T_{RM} proliferation in patients with melanoma (Edwards et al., 2018), and production of high levels of GzmB, TNF-α, and IFN-γ (Djenidi et al., 2015; Ganesan et al., 2017; Behr et al., 2019). However, it has also been reported that T_{RM} isolated from normal human lung tissue may be more effective in effector cytokine production than their counterparts isolated from tumor lung tissue (Bengsch et al., 2018). A tolerogenic signature has been observed in CD8$^+$CD103$^+$ T cells with high expression of IL-10 and CTLA-4 and low expression of TNF-α, IFN-γ, and GzmB in a melanoma mouse model (Gabriely et al., 2017). Nevertheless, T_{RM} are associated with favorable prognosis in many types of human cancer (Table 1). Intriguingly, mouse infection models have recently shown that lung T_{RM} can migrate to the draining LNs (Beura et al., 2018b) and that stimulation of lung T_{RM} led to enhanced responses in the lung-draining LNs (Paik and Farber, 2021). These studies suggest that T_{RM} may coordinate local immunity through fortification of the immune response in the neighboring LNs. If T_{RM} existed in the tumor-draining LNs, T_{RM} would be an ideal cell population to inhibit tumor lymphatic spread and metastases. Collectively, all of the above multifunctional T_{RM} activities make them ideal effector T cells in antitumor immune responses.

T_{RM} in tumor immunotherapy

There is evidence that T_{RM} are involved in tumor immunotherapy. Checkpoint therapy boosts T_{RM} formation in melanoma-bearing mice (Enamorado et al., 2017). PD-1 blockade in combination with T_{CM} transfer results in 10-fold increase in T_{RM} and inhibits B16 and MC38 tumor growth (Enamorado et al., 2017). Consistent with mouse studies, PD-1 blockade of T_{RM} from human non–small cell lung cancer promotes ex vivo cytolysis of T_{RM} to autologous tumors (Djenidi et al., 2015). Anti–PD-1 therapy leads to potent proliferation of CD8$^+$CD103$^+$ T_{RM} in patients with melanoma, and the levels of CD8$^+$CD103$^+$ T_{RM} are associated with improved patient survival (Edwards et al., 2018). Therefore, checkpoint blockade supports the notion that targeting T_{RM} may be therapeutically meaningful. Multiple strategies have been suggested to modulate T_{RM} to enhance cancer therapy efficacy (Fig. 2 and Table 2).

Targeting T_{RM} priming, differentiation, and survival

DC priming is essential for T_{RM} formation in different models, including tumors (Yu et al., 2013; Wu et al., 2014; Iborra et al., 2016; Shin et al., 2016; Enamorado et al., 2017). CD103$^+$ DCs are required for optimal generation of T_{RM} (Iborra et al., 2016). Both CD1c$^+$ DCs (Yu et al., 2013) and CD301b$^+$ DCs (Shin et al., 2016) promote T_{RM} generation from effector CD8$^+$ T cells. Given the importance of DCs in T_{RM} formation, DCs may be used as a vaccine to induce T_{RM}. Furthermore, IL-15 promotes CD8$^+$ T_{RM} in situ (Sowell et al., 2017). Cytokine nanogel allows transference of high doses of IL-15 to the tumor microenvironment (Tang et al., 2018; Xie et al., 2019) and enhancement of the T_{RM} pool in the tumor. Interestingly, Bhlhe40 (a transcription factor) orchestrates T_{RM} survival and functionality and is critical for immunotherapy efficacy (Li et al., 2019). Thus, targeting Bhlhe40 may be an option for cancer immunotherapy. In addition, TGF-β supports T_{RM} formation (Zhang and Bevan, 2013) and promotes radiation resistance of T_{RM} (Arina et al., 2019). Blockade of TGF-β results in reduced numbers of T_{RM} after vaccination (Nizard et al., 2017). Given the general immunosuppressive role of TGF-β, it is challenging to specifically target TGF-β-signaling in T_{RM} to improve cancer therapy. Future studies will determine whether critical and specific potential TGF-β downstream gene(s) for T_{RM} formation can be identified.

Adoptive T_{RM} transfusion

Adoptive transfusion of preprogrammed T_{RM} may be a cancer immunotherapy strategy. Adoptive transfer of tumor-infiltrating T cells with overexpression of Runx3 promotes T_{RM} development, inhibits tumor growth, and improves mouse survival in a melanoma murine model (Milner et al., 2017). T memory stem cells (T_{SCM}) differentiate into T_{RM} (Kondo et al.,

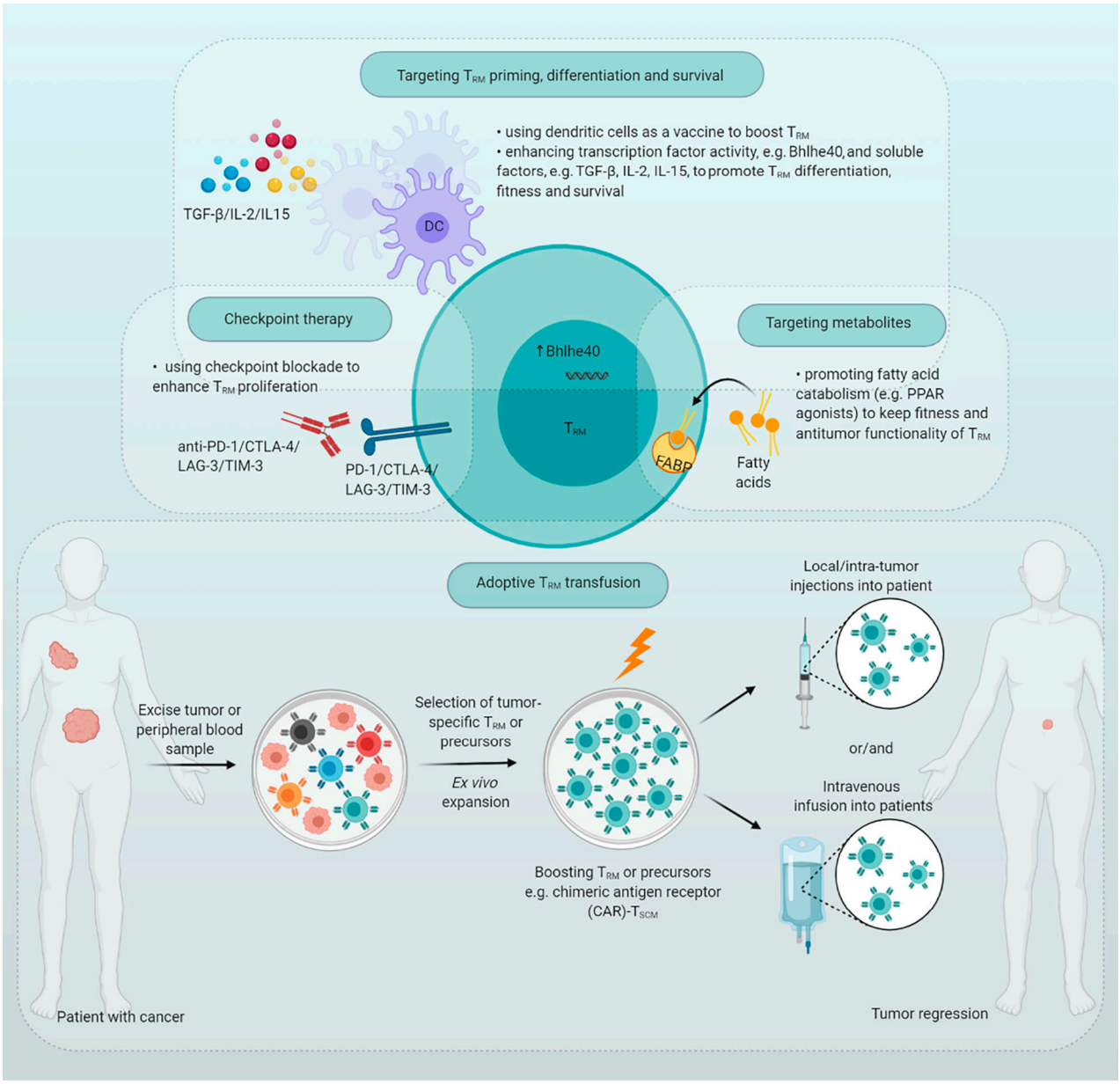

Figure 2. **T_{RM} in cancer immunotherapy.** Several strategies have been proposed to enhance T_{RM} activity. Checkpoint blockade may enhance intratumoral proliferation of T_{RM}. DCs may be used as a vaccine to induce functional T_{RM}. Targeting specific transcription factors and cytokines may drive T_{RM} formation and may boost induction of active T_{RM}. Targeting particular metabolites (e.g., FFA and FABP) may promote T_{RM} pool and antitumor activity. Adoptive transfer of preprogramed T_{RM} or T_{SCM} may improve T_{RM} seeding or differentiation, thereby enhancing antitumor immunity. PPAR, peroxisome proliferator–activated receptor.

2017). Adoptive transfusion of T_{SCM} and chimeric antigen receptor T_{SCM} (Kondo et al., 2020) may lead to increased T_{RM} in cancers. Furthermore, in murine models of melanoma, the presence of both T_{RM} and circulating T cells offers improved protection against tumor challenge compared with only one alone (Enamorado et al., 2017). Thus, adoptive T_{RM} transfusion may be a reasonable approach in combination with other cancer therapies.

Targeting metabolites

T cells compete with tumor cells for glucose, amino acids, and free fatty acids (FFAs; Zhao et al., 2016; Molodtsov and Turk, 2018; Chen and Huang, 2019; Bian et al., 2020, Wang and Zou, 2020). T_{RM} express high levels of FFA-binding proteins FABP4 and FABP5 (Pan et al., 2017; Lin et al., 2020). Peroxisome proliferator-activated receptor agonists promote FFA catabolism, accelerate T cell–mediated antitumor immunity, and sensitize anti–PD-1 treatment (Zhang et al., 2017; Chowdhury et al., 2018). The antitumor effect may be partially attributed to T_{RM} responses. Checkpoint blockade promotes FABP4 and FABP5 expression in T_{RM}, resulting in higher lipid uptake by T_{RM} and enhancing T_{RM} survival (Lin et al., 2020). As such, targeting FFA and FABP can affect T_{RM} and improve antitumor

Table 2. **Role of T_{RM} in cancer immunotherapy**

Tumor types	Treatment strategy	Effects	References
Cervical cancer	Vaccination + radiotherapy	HPV E6/E7-targeted therapeutic vaccination in combination with radiotherapy results in increased intratumoral number of $CD8^+CD103^+$ cells.	Komdeur et al., 2017
Colorectal cancer	Anti–TGF-β mAb + radiotherapy	TGF-β contributes to T_{RM} radioresistance.	Arina et al., 2019
Esophageal cancer	Anti–PD-L1 mAb	PD-L1 blockade increases the number of $CD8^+CD103^+$ cells in the tumor.	Han et al., 2020
Gastric cancer	Anti–PD-L1 mAb	PD-L1 blockade increases FABP4 and 5 expression in T_{RM}, favoring lipid uptake by T_{RM} and resulting in improved cell survival.	Lin et al., 2020
		PD-L1 blockade unleashes T_{RM} in the PDX mice.	
		Non-responder PDX mice to PD-L1 blockade have less T_{RM} than responders.	
Head and neck cancer	Vaccination, anti–TGF-β mAb	STxB-E7 vaccination induces T_{RM} and inhibits tumor growth.	Nizard et al., 2017
		TFG-β blockade inhibits T_{RM} formation after vaccine immunization, resulting in lower vaccine efficacy.	
Melanoma	"Prime-boost" immunization (CpG ODN 1826, OVA)	Subcutaneous antigen injection and epicutaneous CpG ODN adjuvant administration correlate with enhanced numbers of $CD103^+CD8^+$ cells in the skin, enhance T_{CIRC} in the blood, and prevent tumor development.	Lai et al., 2019
	Vaccination (pVAX-OVA/DNA-OVA and pcDNA-GP100/DNA-GP100)	Vaccination-induced T_{RM} strongly suppress the growth of melanoma cells independently of T_{CIRC}.	Gálvez-Cancino et al., 2018
	Anti–PD-1 mAb (nivolumab, pembrolizumab)	$CD103^+$ cells significantly expand early during treatment.	Edwards et al., 2018
	Adoptive T cell transfer	Runx3-deficient $CD8^+$ cells fail to infiltrate the tumor, resulting in higher tumor growth and mortality.	Milner et al., 2017
		Runx3 overexpression enhances $CD8^+$ cell tumor infiltration, inhibits tumor growth, and prolongs OS.	
	T reg depletion and tumor removal	Skin-resident T_{RM} are necessary for rejection of tumor rechallenge and long-lived melanoma immune protection.	Malik et al., 2017
	Adoptive T cell transfer, anti–PD-1 mAb	Anti–PD-1 boosts T_{RM} tumor infiltration and improves antitumor immunity after T_{CM} transfer.	Enamorado et al., 2017
	Anti-CD103, anti–VLA-1 mAb	Blockade of CD103 or VLA-1 on T_{RM} impairs tumor control.	Murray et al., 2016
	Adoptive T cell transfer, anti-CD103 mAb	Transfer of $CD8^+CD103^+$ cells enhances tumor growth, whereas CD103 blockade inhibits tumorigenesis.	Gabriely et al., 2017

HPV, human papillomavirus; ODN, oligodeoxynucleotide; OS, overall survival; PDX, patient-derived xenograft; STxB, B subunit of Shiga toxin; T_{CIRC}, circulating memory T cells; VLA-1, very late antigen 1.

immunity. Future studies will generate insight into T_{RM} metabolic features and how to target T_{RM} metabolism for cancer therapy.

Conclusions

Current evidence shows that T_{RM} can evoke potent antitumor immune responses. However, our understanding of their phenotype, differentiation, trafficking, tissue retention, and effector function remains in its infancy. This is particularly the case in patients with cancer. Substantial human studies rely on expression of CD49, CD69, and CD103 to define T_{RM}. A number of mouse tumor-bearing models and human samples have revealed the presence of T_{RM} phenotype cells within tumors. These T_{RM} may arise de novo from the tissue or infiltrate as part of the antitumor immunosurveillance. Evidence thus far shows that T_{RM} presence in a tumor or in response to immunotherapy can be a useful prognostic indicator for improved outcomes. Using high-throughput technologies, including single-cell sequencing, microscopic tissue spatial analysis, and multi-omics studies, we may be able to fruitfully study limited clinical materials to gain critical and novel information on T_{RM}, leading to developing new cancer treatments via targeting T_{RM}.

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