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Egress of resident memory T cells from tissue with neoadjuvant immunotherapy: implications for systemic anti-tumor immunity

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Abstract

Introduction: Resident memory T (T_{RM}) cells are embedded in peripheral tissue and capable of acting as sentinels that can respond quickly to repeat pathogen exposure as part of an endogenous anti-microbial immune response. Recent evidence suggests that chronic antigen exposure and other microenvironment cues may promote the development of T_{RM} cells within solid tumors as well, and that this T_{RM} phenotype can sequester tumor-specific T cells into tumors and out of circulation resulting in limited systemic antitumor immunity. Here, we perform a review of the published English literature and describe tissue-specific mediators of T_{RM} cell differentiation in states of infection and malignancy with special focus on the role of TGF-β and how targeting TGF-β signaling could be used as a therapeutical approach to promote tumor systemic immunity.

Discussion: The presence of T_{RM} cells with antigen specificity to neoepitopes in tumors associates with positive clinical prognosis and greater responsiveness to immunotherapy. Recent evidence indicates that solid tumors may act as reservoirs for tumor specific T_{RM} cells and limit their circulation – possibly resulting in impaired systemic antitumor immunity. T_{RM} cells utilize specific mechanisms to egress from peripheral tissues into circulation and other peripheral sites, and emerging evidence indicates that immunotherapeutic approaches may initiate these processes and increase systemic antitumor immunity.

Conclusions: Reversing tumor sequestration of tumor-specific T cells prior to surgical removal or radiation of tumor may increase systemic antitumor immunity. This finding may underlie the improved recurrence free survival observed with neoadjuvant immunotherapy in clinical trials.

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Declaration of interests

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Introduction

One of the hallmarks of adaptive immunity is the capacity for memory, which enables rapid clearance of pathogens upon re-exposure to the initial antigen[1]. T cells that remain after being licensed by the primary antigen exposure exist as central, effector, and resident memory T cell subsets (T_{CM}, T_{EM}, and T_{RM}, respectively) and occupy different anatomic spaces where they fulfill distinct roles in protective immunity[2,3]. T_{RM} cells are classically described as non-recirculating memory T cells that remain positioned at common sites of re-exposure, including barrier tissues such as the skin[4] and mucosa[5]. In these barrier tissues, abundant CD4 and CD8 T_{RM} clonotypes that target a variety of antigens can be found[6,7]. These tissue-retained T cells are distinguished by expression of the integrins CD69[8,9] and CD103[10,11]. CD69 is a membrane-bound type II C-lectin receptor that acts primarily via S1PR1 (Sphingosine-1-Phosphate Receptor 1) to promote tissue residency[8,9]. S1PR1 receptor signaling overrides retention mediated by G alpha i-coupled receptors. CD69, whose expression is rapidly induced on the surface of T lymphocytes following T cell activation, binds the S1PR1 receptor to induce receptor activation and internalization without lipid ligands, thus promoting retention[12,13]. Integrin, alpha E (ITGAE), also known as CD103, is highly expressed at mucosal sites and binding to E-cadherin promotes retention in peripheral tissues[14]. Other markers such as CD49a[15,16] and CD44[17,18] have also been extensively explored to distinguish T_{RM} cells from other T cell subsets, both in mice and humans. CD44 is a type I transmembrane glycoprotein that has long been used to differentiate memory and effector T cells from their naïve counterparts[19]. CD49d/α4-integrin is selectively expressed in mucosal endothelium and mediates both cellular rolling and firm adhesion by binding MCAM-1, thus functioning as a T cell retention receptor in mucosal lymphoid tissues[20,21]. Local tissue environments supply a diverse array of cytokines[22,23] that mediate expression of distinct chemokine receptors such as CCR8 in the skin[24] and CXCR6 in respiratory epithelium[25] that contribute to maintenance of a tissue residence phenotype in T cells. T_{RM} cells undergo a distinct differentiation program that discriminates them from circulating T_{CM} cells and T_{EM} cells[4,26,27] even when these subsets share a common progenitor, as evidenced by T cell receptor (TCR) repertoire overlap in distinct tissue compartments[28,29].

This tissue resident program develops to populate barrier tissues such as skin and mucosa with highly protective T cells specific against the pathogens most commonly present in those environments. Importantly, similar T_{RM} cell phenotypes have also been observed in solid tumors and found to be enriched in T cell clonotypes specific for tumor antigens[30]. Therefore, a better understanding of the cues that drive the development of a T_{RM} cell phenotype amongst tumor-infiltrating T cells and the implications of such programs on the compartmentalization of anti-tumor immunity is needed. For example, if development of a T_{RM} cell phenotype occurs upon chronic TCR stimulation and cytokine cues in tumors such that the tumor acts as a reservoir for a significant proportion of the tumor specific T cells in a patient, definitive surgical removal or radiation ablation treatment may remove most of the patient's antitumor immunity. Here we discuss the environmental factors and transcriptional programming steps that drive the differentiation of naïve T cells to a T_{RM} cell phenotype, with a specific focus on $CD8^+$ T cells and the role of the multi-functional

cytokine transforming growth factor-beta (TGF-β), summarized in Figure 1. We additionally discuss existing evidence suggesting that tumor specific T cell tumor residency can be therapeutically manipulated, and the clinical implications of these observations.

Review Methods

Literature was identified by searching PubMed for “resident memory T cell” in combination with terms including differentiation, immunotherapy, cancer, and recirculation, searching publication dates from March 1993 to March 2023. Both pre-clinical and clinical reports were included. The relative contribution of reach report was described within the context of the larger field along with additional questions that it raised. One reviewer independently screened each report and synthesized findings, which were verified by all authors.

Discussion

TGF-β and other mediators of T_{RM} differentiation

The tissue resident memory programming may be initiated in draining lymph nodes (dLN) when dendritic cells (DCs) present naïve T cells with antigens from the initial site of exposure[31]. Before migrating out of the dLN and entering circulation, activated T cells undergo extensive proliferation in the days following antigenic exposure[32]. Yoon and colleagues reported that activated $CD8^+$ T cells undergo up to 5–6 divisions within 2–4 days post antigen encounter[32]. More recently, Kurd *et al.* performed a time course experiment in LCMV-infected mice and, using single-cell RNA-sequencing (scRNA-seq) to track individual T cell clonotypes over time and location, were able to identify rapid induction of a T_{RM} signature in T cells that traffic into peripheral tissues[33]. There is some evidence, although, that $CD8^+$ T cells can be preconditioned in the dLN for T_{RM} differentiation upon interaction with integrins on migratory DCs[34]. Another study tracing lineage patterns of adoptively transferred barcode-labeled ovalbumin-specific transgenic $CD8^+$ T (OT-I) cells in immunized mice found a subset of antigen-specific $CD8^+$ effector T cells that began expressing a T_{RM} transcriptional signature while still in the dLN[35]. This demonstrates the potential for $CD8^+$ T cells to commit to a memory and possibly tissue resident fate prior to peripheral tissue entry. Acquisition of a T_{RM} cell phenotype in a subset of $CD8^+$ T cells upon entry into peripheral tissues is well established, but whether commitment to T_{RM} cell fate necessarily begins in the dLN priming phase requires further investigation.

The T_{RM} program in peripheral tissues is promoted by engagement with chemokine receptors that drive expression of adhesion molecules like integrins[36–39]. After initial chemotaxis to tissues mediated at least by the chemokines CXCL9 and CXCL10[40], T cell tissue entry begins when signals such as IL-1[41], TNFα[41–43], LPS[44], and IL-4[42] promote expression of the cell adhesion molecules E-selectin and P-selectin on endothelial cells at site of active inflammation that facilitate rolling and firm adhesion within vessels. Following T cell extravasation through a process that requires at least CD44[45], T cells within tissues are exposed to TGF-β secreted by fibroblasts, epithelial cells, and leukocytes[46,47]. TGF-β promotes tissue residency by upregulating adhesion molecules including the integrins CD103[14,48,49], αEβ7, α1, CD69[48], αvβ6, αvβ8[50], and CD49a[16]. Interestingly, IL-12, which has also been reported to induce CD49a *in vitro*[16], negatively affects the expression

of CD103[51,52]. This might help explain why IL-12, together with IFN-β, in highly proinflammatory microenvironments promotes the differentiation of a subset of T_{RM} cells that are phenotypically $CD103^{-}CD69^{+}$[23]. $CD103^{-}$ CD8 T_{RM} cells develop in the intestinal LP where they cluster in areas of infection together with other inflammatory immune cells such as $CX3CR1^{+}$ macrophages and dendritic cells[22]. Of note, $CD103^{-}$ T_{RM} cells seem to display distinct functional capabilities and tissue specificities when compared with their $CD103^{+}$ counterparts. $CD103^{-}$ T_{RM} cells display a transcriptional profile similar to circulating T cells and display higher migratory potential, making them the primary responders in sites of secondary infection[53]. Consequently, $CD103^{-}$ T_{RM} cells exhibit more plasticity, being capable of modifying their phenotype following migration, whereas $CD103^{+}$ T_{RM} cells may be more resistant to transdifferentiation[54].

Recent work has also highlighted the importance of TGF-β signaling in maintaining a subset of stem-like $CD8^{+}$ T cells that is crucial for long-term T cell response in tissues[55–57]. These cells, termed precursor of exhausted T cells (T_{PEX}), have a high proliferative capacity in lymphoid tissues where its progeny is committed to an exhausted T cell fate. Although they share functional similarities with $CD8^{+}$ memory T cells formed during acute infection, chronic antigen exposure enforces a distinct transcriptional and epigenetic program that characterizes this population as $TCF\text{-}1^{+}PD\text{-}1^{+}CXCR5^{+}Tim\text{-}3^{lo}$[58–61]. In a model of chronic LCMV infection, parabiosed mice were used to track virus-specific $CD8^{+}$ T cells, leading to the observation that stem-like T_{PEX} $CD8^{+}$ cells proliferated in LNs to give rise to terminally differentiated progeny that formed a resident memory population. Unlike in the acute setting, there was minimal trafficking of stem-like cells between mice, which further supports the concept of acquired residency[62]. Using a mouse model of melanoma, Li *et al* demonstrated that TGF-β signaling was the main driver of differentiation of tumor-specific stem-like $CD8^{+}$ T cells into T_{RM} phenotype in the tumor dLN. Furthermore, the authors were able to show that stem-like $CD8^{+}$ T cells also differentiate into T_{RM}-like cells in dLN of human head and neck squamous cell carcinoma (HNSCC) patients[56]. These $TCF1^{+}$ tumor specific $CD8^{+}$ T cells seem to maintain antitumor responses by giving rise to effector cells that take up residency in tumors[63,64]. They expand in the dLN and traffic to the tumor[63] or proliferate in regions of the tumor that are enriched with antigen presenting cells (APCs)[64], processes that involve TGF-β-mediated upregulation of CD103. Clearly TGF-β plays a crucial role in the development of T_{RM} phenotype once activated T cells enter peripheral tissues, such as skin and mucosa.

T_{RM} transcriptional program

The transcriptional signature of T_{RM} cells was initially established through adoptive transfer of gBT-I cells, which express a transgenic TCR specific for herpes simplex virus (HSV), into HSV-immunized mice. Microarray analysis of $CD103^{+}$ gBT-I cells isolated from skin epithelium revealed that T_{RM} cells develop from $KLGR1^{-}$ precursors that upregulate CXCR3[27]. KLRG1 (Killer Lectin-like Receptor G1) is a co-inhibitory receptor that has been used to identify antigen-experienced T cells and to distinguish memory precursor cells from effector T cells[65]. During effector differentiation, CD8 T cells gain expression of KLRG1. KLRG1 is then downregulated as cells further differentiate into memory T cell lineages, including T_{RM} cells, a process mediated by the transcriptional repressor Bach2. In

the gBT-I model, after entering the epidermis, KLGR1^{-} precursors are signaled by TGF-β and IL-15 to enhance retention and survival of T_{RM} cells by promoting CD103 and Bcl-2 expression, respectably[27]. A transcriptional analysis comparing circulating T_{EM} and T_{CM} cells to different T_{RM} subsets revealed that T_{RM} cells selectively upregulate the expression of the aryl hydrocarbon receptor (Ahr) which acts as a promoter of T_{RM} cell differentiation and function[66], the G protein signaling genes RGS1 and RGS2 that modulate T cell trafficking[67], and the receptor of the immunoglobulin (Ig) superfamily CD244 (SLAMF4; 2B4), known to increase tissue infiltration of not only CD8^{+} T cells but also dendritic cells (DCs) and myeloid-derived suppressor cells (MDSCs)[68]. Inversely, the authors found that the transcriptional signature was characterized by the downregulation of S1PR1 and Fam65b[69], an inhibitor of the small GTPase RHOA[70]. Interestingly, expression of both S1PR1[71] and Fam65b[69] has been shown to be negatively affected by TGF-β signaling. As mentioned, at the protein level, surface expression of S1PR1 is disabled upon forming a complex with CD69[13,72]. In HSV-immunized mice, adoptively transferred gBT-I cells with deficient CD69 expression (CD69$^{-/-}$) failed to maintain tissue residency to the same extent as wildtype cells, but upon treatment with the S1P receptor agonist, FTY720, accumulation of CD69$^{-/-}$ cells in infected skin was restored[13]. Transcriptionally, CD8 T_{RM} cells in the parenchyma of non-lymphoid tissues (NLTs) have also been shown to lack expression of the transcription factor KLF2 and its target *S1pr1*[73]. These two different mechanisms highlight the importance of S1PR1 downregulation for tissue retention and maintenance of long-term immunity in peripheral tissues.

Although the transcriptomic signature of T_{RM} cells is heterogenous across tissues[74], several transcription factors have been identified as master regulators of T_{RM} cell fate. The T-box transcription factors Eomesodermin (Eomes) and T-bet, for instance, have been described as key regulators of T_{RM} cell differentiation[75,76]. Eomes seems to play tissue-specific roles, having been reported to repress T_{RM} cell formation in the skin, liver, and kidney[75,77], while supporting maintenance of established T_{RM} cells in the small intestine, partially by inducing the antiapoptotic molecule Bcl-2[78]. T-bet, whose expression is proportional to the strength of the TCR signaling, has been widely described to promote T_E/T_{EM} formation[79] and suppress T_{RM} cell differentiation[75]. Like T-bet, the transcriptional repressor Blimp1 is also upregulated by inflammation and/or TCR triggering. However, contrary to T-bet, Blimp1 works to maintain the T_{RM} phenotype while also being able to promote the differentiation of T_E/T_{EM} cells[80–82]. T-bet also mediates the expression of the transcription factor Hobit, which is jointly upregulated with Blimp1 to promote T_{RM} cell differentiation[80,82,83]. *Hobit* has been found to be upregulated in a subset of LCMV-specific CD8^{+} T cells located within peripheral tissues that were identified to be T_{RM} cell precursors, since depletion of these cells substantially decreased T_{RM} cell development[77]. Hobit, as Blimp1, was shown to bind and regulate the expression of *Tcf7*, *S1pr1*, *Klf2* and *Ccr7*, and loss of these transcription factors might enable T_{RM} cells to leave the tissue and re-enter circulation[77]. Hobit and Blimp1 are at the core of transcriptional program of tissue residency, mostly working together but with some exceptions, as is the case for the differentiation of CD8+ T_{RM} cell in the lungs which has been reported to exclusively dependent on Blimp1[84]. KLF2 is a member of the Krüppel-like transcription factor family of proteins that directly controls the expression of CD62L and $S1P_1$[85]. KLF2 is downregulated during T_{RM} cell

development, leading to decreased expression of $S1P_1$ and facilitating the retention of these cells in peripheral tissue[11,71,86]. More recently, the transcription factor Runx3 has also been shown mediate T_{RM} cell differentiation and survival[87,88]. In a murine melanoma model, adoptively transferred tumor specific $CD8^+$ T cells deficient in Runx3 were unable to maintain tumor residency resulting in uncontrolled tumor growth[88]. Interestingly, Runx3 enforces tissue residency of $CD8^+$ T cells through the promotion of chromatin accessibility at TGF-β regulated genes[88]. Another regulator of the T_{RM} cell formation that acts on the TGF-β-driven residency program is the SKI proto-oncogene. SKI negatively regulates TGF-β signaling by directly interacting with Smads and repressing the transcription of TGF-β responsive genes such as CD103[89].

In addition to these highly conserved pathways, tissue-specific transcriptional regulators of T_{RM} cells have been identified by comparing gene expression patterns of tissue isolated from different compartments of immunized mice. In the small intestinal epithelium, unique regulators include Nr4a2, Junb, Fosl2[33] and Hic1[76]. In the respiratory epithelium, signaling through the TNF receptor family members CD137 (4–1BB)[90] and GITR[91] is required for the generation of $CD4^+$ and $CD8^+$ T_{RM} cells.

T_{RM} cells can, therefore, be identified using certain core transcriptional signatures and several cell surface protein markers. However, some circulating T cells also express genes associated with tissue-residency at levels comparable to T cells infiltrating NLTs, including canonical T_{RM} markers such as *CXCR6*, *CD69* and *ITGA1*[11,92,93]. A key feature that distinguishes T_{RM} cells in tissue from T_{RM}-like cells in circulation may be their functional status. Recently, Noé and colleagues investigated liver-infiltrating T_{RM} cells following malaria prime-target vaccination (PTV) and compared them to $CD69^+$ T_{RM}-like circulating cells and found that both subsets shared expression of conventional-residency markers but differed metabolically and functionally[94]. Specifically, T_{RM}-like cells in circulation upregulated the zinc transporter *SLC39A7* and were metabolically active, while tissue infiltrating T_{RM} cells were metabolically quiescent but ready for rapid effector function upon activation. As such, although T cells expressing markers associated with tissue residency can be found both in tissue and in circulation, these cell population may be distinguished from each other functionally.

Recirculation of T_{RM} cells

Although T_{RM} cells were initially portrayed as T lymphocytes permanently embedded in nonlymphoid peripheral tissue like skin and mucosa, under certain conditions T_{RM} cells can leave the tissue of residency and recirculate[95,96]. Often these circulating T_{RM} cells are described as ex-T_{RM} cells and express some EM phenotype markers such as KLRG1 and CX3CR1[97]. In murine models, local restimulation of T_{RM} cells results in the egress of cells from tissues of residency[97–99]. Using a (VSV)-expressing ovalbumin (VSVova) infection model and resorting to skin-grafts, Fonseca *et al.* demonstrated that upon reactivation of T_{RM} cells within the previously immunized mice, OT-I cells started accumulating in the dLN and circulating OT-I cells with T_{CM} and T_{EM} signatures were observed in distant LNs 2–3 weeks later[98]. This data indicates that T_{RM} cells are capable of not only tissue egress, but also transdifferentiation into other memory phenotypes in circulation, which is suggestive of

developmental plasticity. Behr and colleagues also observed recirculation of tissue-resident OT-I cells that developed after oral infection with *Listeria monocytogenes*-expressing OVA (Lm-OVA). Hobit expression, which is necessary to enact the T_{RM} program in T cells within this model, was downregulated following secondary antigen recognition[97]. Consequently, reduced or abrogated Hobit expression following T_{RM} cell reactivation might be crucial for T_{RM} cell tissue egress and differentiation into other T cell phenotypes in circulating cells.

Another example of systemic immunity arising from egressed T_{RM} cells comes from the work of Klicznik *et al*[100]. Using transcriptional profiling of rare cell populations by RNA sequencing (RNA-seq) the authors were able to identify a population of skin T_{RM} $CD4^+$ T cells that recirculate through blood and thoracic duct lymphatics in the steady state. These $CD4^+$ T cells express the cutaneous lymphocyte antigen (CLA), characteristic of skin–resident memory T cells, together with CD103, and their exit from tissue was associated with downregulation of CD69. Interestingly, these circulating $CD4^+CLA^+CD103^+$ T_{RM} cells were able to reseed distant skin sites, regaining CD69 expression upon reentering the tissue[100]. The Klicznik work did not definitively identify the mechanism of egress of T_{RM} cells from the skin, but a later study proposed that regular tissue-damaging conditions result in the activation of T_{RM} cells and subsequent emigration. Specifically, this study observed an increased percentage of circulating T_{RM} cells of skin origin in the blood of patients with graft-versus-host disease (GVHD) and cutaneous infections, implicating local inflammation in re-activation and tissue egress of TRM cells[101].

Tissue residency in malignancy

In addition to their role in pathogen defense, cells phenotypically similar to T_{RM} have been identified within epithelial malignancies (carcinomas) where they constitute an important part of the antitumor immune response. The gene expression signature of subset of CD4+ and CD8+ T cells infiltrating carcinomas parallels that of T_{RM} cells present in healthy barrier tissue like skin and mucosa[30], with these tumor infiltrating lymphocytes (TILs) expressing CD103 and CD69[102,103]. However, chronic antigen persistence in the tumor results in a fundamentally different microenvironment compared to the setting of resolution of infection and inflammation where classic T_{RM}s have been described. Chronic TCR signaling and other features such as TGF-β exposure in tumors drive a transcriptional program in T cells that shares hallmark features of T_{RM} generated after infection[104]. To date, these CD103+ TILs have mostly been described simply as T_{RM} cells, but recent evidence suggests that they may more accurately be referred to a 'T_{RM}-like' cells[105–107].

Steele and colleagues demonstrated that TCR affinity may play an important role in the accumulation of $CD8^+$ T cells in tumors[108]. In their study, interaction with high-affinity antigens, but not low-affinity, led to the downregulation CXCR4 and upregulation of the CXCL12 decoy receptor, ACKR3. CXCR4 is a chemokine receptor that binds to CXCL12, also known as SDF-1, which is produced by Bone Marrow (BM) stroma, thus functioning as a homing signal to the BM[109]. CXCR4 expression can therefore prevent infiltration of T cells into tumors because the surrounding stroma expresses CXCL12.[110] In the YUMMER1.7 mouse melanoma model, reduction in the sensitivity to CXCL12 promoted T cell tumor infiltration and improved tumor control in the context of PD-L1 immunotherapy.

Objectively, entry of T cells into tumors seems to be a critical step in the development of an effective T cell response.

Accumulation of T_{RM} cells in tumors is associated with increased survival[30,103,111] and positive response to immunotherapies, including anti-PD-1 and anti-CTLA-4 immune checkpoint blockade (ICB)[112,113]. Immunotherapy strategies such as ICB may reverse an exhausted (and dysfunctional) state in T cells caused by chronic antigen exposure, characterized by the expression of high levels of the inhibitory receptors PD-1, Lag-3, TIM-3, CTLA4, and Tigit[114–117]. Indeed, gene expression programs indicating exhaustion and tissue residency appear to be closely associated in tumor specific T cells. Although it is clear that the development of exhaustion and tissue residency gene expression programs occurs downstream of TCR signaling[118], additional understanding of the complex similar or dissimilar signals from the tumor microenvironment that drive either program are needed and may help inform the development of novel therapeutics beyond immune checkpoint blockade that modulate one or both programs.

Examples of the importance of T_{RM}-like cells in response to ICB exist across several cancer types. In a non-small cell lung cancer (NSCLC) patient cohort, Djenidi *et al.* demonstrated that $CD8^+$ tumor-infiltrating lymphocytes (TIL) upregulate genes encoding adhesion molecules including CD69, CD103, RGS1, ICOS1 and downregulate egress mediators $S1P_1$ and ITGB2. Besides markers of residency, these TILs also acquired the expression of PD-1 and Tim-3[30], consistent with the idea of persistent antigen exposure and T cell exhaustion in the tumor microenvironment (TME). Furthermore, the authors observed that the presence of $CD103^+$ TILs associated with increased survival of early-stage NSCLC patients and that neutralization of PD-1–PD-L1 interactions improved the specific cytotoxic activity of $CD8^+CD103^+$ T cells against autologous tumor cells[30]. In early stage primary triple negative breast cancer, enrichment in $CD8^+CD103^+$ T_{RM} cells has also been associated with improved overall survival after standard chemotherapy[111]. In their study, Savas and colleagues only reported on the contribution of infiltrating T cells to clinical outcomes, but more recently Egelston *et al.* suggested that this effect may be mediated by enhanced infiltration into the tumor parenchyma rather than the stroma by a subset of $CD8^+CD103^+$ TILs relative to their $CD103^-$ counterparts[119]. Hence, spatial localization of $CD8^+CD103^+$ TILs within cancer islands is an important determinant of patient survival.

In patients with hepatocellular carcinoma, pre-treatment biopsies with a higher proportion of $CD8^+$ T_{RM} cells to exhausted $CD8^+$ T (T_{EX}) cells demonstrated enhanced responsiveness to anti-PD-1 therapy[113]. Similarly, in patients with advanced stage melanoma, pre-treatment enrichment of $CD8^+$ T_{RM} cells in the tumor was associated with responsiveness to immune-checkpoint blockade (ICB) and recurrence free survival (RFS). Multiplex immunohistochemistry showed that $CD8^+$ T_{RM} cells localized in closer proximity to melanoma cells compared to other $CD8^+$ T cells, supporting the idea that spatial localization matters for cytolytic effects[112].

Quantity, however, is not the only determinant of improved prognosis. Quality, particularly diversity of T cell specificity, is also a crucial aspect of T_{RM} cells association with favorable clinical outcomes. T cell responses depend on antigen recognition and the type of tumor

antigens presented by cancer cells may shape the TCR repertoire observed. Notably, evaluation of the TCR repertoire of TILs has been a major focus of predictive work in cancer prognostics[120–122]. TCR repertoire analysis of $CD8^+$ T cells within the mucosa of patients with gastric cancer revealed a positive association between clonotype diversity and survival[123]. In patients with pancreatic cancer, repertoire diversity has been linked to enhanced survival following neoadjuvant therapy and surgical resection[124]. The degree of clonal infiltration is not a one-size-fits-all phenomenon, with tumor control being shaped by the functional attributes of tumor-specific TILs. In ovarian cancer, Tsuji *et al.* found that favorable prognosis was associated with strong monoclonal TCR repertoires[125]. This might be due to the presence of a significant number of bystander TILs that recognize non-cancer antigens[103]. In patients with metastatic melanoma, TCRs with neoantigen specificity are more likely to be identified amongst clonotypes present in higher frequencies[126]. Investigation of the TCR repertoire of $CD8^+$ T cells that harbor a T_{RM} phenotype has thus facilitated the identification of TCR clones that recognize tumor-associated (TAAs) and tumor-specific (TSAs) antigens.

Building systemic immunity against cancer through egress of T_{RM} cells

As in the setting of infection, recirculated T_{RM}-like cells may have the potential to confer enhanced protection against distant disease or locoregional disease relapse. Given this potential, mechanisms that regulate T cell trafficking are of interest since enhanced systemic antitumor immunity could be achieved by egress of T_{RM} cells from the primary tumor or dLN prior to surgical removal or radiation ablation. Initially, responsiveness to ICB was related to early expansion of circulating $CD8^+$ T_{EM} with diverse repertoire clonality[127–130]. Recent studies suggest that ICB can also induce the egress of reinvigorated, exhausted, T_{RM}-like cells. In a study by Luoma and colleagues, tumor-infiltrating $CD8^+$ T cells that expressed elevated tissue-resident memory and cytotoxicity signatures clonally expanded during neoadjuvant anti-PD-1 or anti-PD-1/CTLA-4 immunotherapy. Treatment also resulted in the identification of increased frequencies of the same tumor-infiltrating $CD8^+$ T cell clonotypes in the blood of the patients after treatment compared to before, demonstrating that ICB therapy may drive egress of tissue-infiltrating $CD8^+$ T cells and enhance systemic immunity[95]. More recently, in a neoadjuvant immunotherapy clinical study using dual PD-L1 blockade and TGF-β neutralization, Sievers *et al.* demonstrated expansion of antigen-specific exhausted and proliferating T cells that harbored markers of residency including CD103[96]. Dual PD-L1 blockade and TGF-β neutralization reduced intratumoral expression of CD103, a TGF-β-induced integrin whose downregulation was validated *in vitro* to be linked to TGF-β neutralization. This treatment established a pool of neoepitope-specific $CD8^+$ T cells that were undetectable in the blood prior to treatment. Whether tumor specific T cells identified at greater frequency in circulation after treatment with ICB egress form the primary tumor, tumor dLN or both, requires further study. Concomitantly, whether TGF-β neutralization is required in addition to ICB to facilitate efficient egress of T_{RM} cells from peripheral tissues into circulation or whether this can be achieved with ICB alone also requires further study. Figure 2 illustrates the concept of using immunotherapy to induce recirculation of T_{RM}-like cells in patients with cancer prior to surgical removal.

These findings have important clinical implications because $CD8^+$ T_{RM} cells, at least in the context of prior infection, have the potential to sustain a long-term systemic antitumor immunity[131,132]. Some early evidence exists that this may also be true for T_{RM} cells that develop in the contact of malignancy. In a patient with dormant metastatic melanoma, $CD8^+CD103^+$ T cells were enriched in micrometastases near melanoma cells, providing control of cancer growth[131]. In a patient with vaginal melanoma refractory to ICB, tumor specific $CD8^+$ T_{RM} cells were found only in metastatic lesions that shared TCRs with T_{EM} in the primary tumor. Although the isolated $CD8^+$ T_{RM} cells showed strong functional responsiveness to melanoma antigens *in vitro*, loss of major histocompatibility complex (MHC) class I expression blunted tumor responsiveness *in vivo*[133]. In a cohort of patients with metastatic melanoma who had a durable response to immunotherapy, scRNA-seq and paired scTCR-seq were performed across tissues at time points that spanned up to 9 years. Interestingly, tumor-reactive clonotypes were found not only as T_{RM} clones in the tumor and distant skin, but also as T_{EM} cells in circulation[132] . This supports a growing body of literature indicating that T_{RM} cells expand locally in response to ICB, but then traffic through the blood to confer systemic antitumor immunity[95,134]. How ICB alters tissue retention of other T_{RM} cells in non-malignant tissue (intestines, for example) remains to be determined.

Another route of protection against metastasis may be driven by precursor cells that differentiate into T_{RM} cells following recirculation from the tumor. Using a murine model of triple negative breast cancer (TNBC), Christian *et al.* performed TCR-β repertoire sequencing on $CD8^+$ T cells isolated from the tumor and benign distant tissues and found that T_{RM} clonotypes in the distant tissue that overlapped with those in the tumor shared developmental ontogeny. The distant mucosal T_{RM} cells originated from a subset of $CXCR6^-$ intratumoral effector T cells (T_{eff})/ T_{EM}[135]. CXCR6 promotes tissue residency through interaction with its unique ligand CXCL16 expressed by epithelial cells[136], and immune cells such as dendritic cells (DCs)[137]. Disrupting CXCR6-mediated retention through intratumoral injection of a CXCL16 neutralizing antibody resulted in the reduction of the metastatic disease burden in distal tissues[135]. This suggests that a subset of tumor infiltrated T_{eff}/T_{EM} cells retains potential to egress from tumors and fully differentiate into T_{RM} cells at distant sites, thereby conferring protection from metastasis.

In a study using a mouse model of melanoma-associated vitiligo, Molodtsov and colleagues[138] demonstrated that the presence of $CD8^+$ T_{RM} cells in regional lymph nodes confers immunity to metastatic melanoma. Through scRNA sequencing, the authors found that some of the most expanded clonotypes in vitiligo-affected skin also occurred in the LNs where they were overwhelmingly maintained as T_{RM} cells. In turn, these $CD8^+$ T_{RM} cells afforded long-lived protection against melanoma seeding in LNs. They further expanded these findings to humans, finding $CD8^+CD69^+$ T cells within human melanoma-infiltrated sentinel lymph nodes (SLNs) that exhibited T_{RM} features[138]. This suggests that the potential to generate T_{RM} cells in the SLNs of melanoma patients could confer protection against metastasis.

The clinical implications of T_{RM} cells in cancer

Multiple independent reports now indicate that tumor specific T cells harboring a T_{RM} phenotype are sequestered in solid tumors and likely dLN and are present at very low frequencies or undetectable in circulation in patients with cancer[95,96]. If this reservoir of tumor specific T cells in the tumor and dLN is removed with surgery or ablated with radiation treatment, a significant proportion of the patient's antitumor immunity could be lost. Multiple reports also indicate that peripheral blood frequencies of tumor specific T cells that display a T_{RM} phenotype in the tumor can be substantially increased with ICB-based immunotherapy prior to definitive treatment[95,96]. Additionally, multiple lines of pre-clinical and clinical evidence suggest that enhancement of systemic anti-tumor immunity confers protection against disease relapse or metastasis[131–133,135]. Together, these data indicate that for patients with newly diagnosed cancer, tissue egress and re-circulation of tumor specific T_{RM} cells may underlie the substantially improved recurrence free survival observed in patients that receive neoadjuvant ICB. Proceeding with definitive surgical resection or radiation treatment without first activating and inducing tissue egress of tumor specific T_{RM} cells into circulation may remove a substantial proportion of the patient's antitumor immunity and reduce the chance of long-term relapse free survival. In addition to surgical stress[139] and surgery associated NK cell dysfunction[140], reduced systemic antitumor immunity after surgical removal of a tumor harboring tumor specific T_{RM} cells may also result from so called 'surgery-induced immunosuppression', which is consistent with observations of outgrowth of metastatic deposits following removal of a primary tumor across many cancer types[141].

The rationale for aiming to therapeutically induce T_{RM} cell egress from primary tumors into circulation may be clinical context dependent. For example, inducing tissue egress of tumor specific T_{RM} cells from tumors and dLN into circulation may be desirable in patients with newly diagnosed cancer to maintain systemic anti-tumor immunity following definitive surgical resection or radiation ablation, but may be undesirable in a patient with relapsed disease where the goal is to maintain the greatest possible density of tumor specific T cells within disease deposits. Accordingly, use of therapeutic interventions that aim to induce tissue egress of T_{RM} cells into circulation may have the strongest scientific rationale in the neoadjuvant or induction setting.

Conclusions

Recognition of compartmentalization of tumor specific T cells into tumors through induction of a T_{RM}-like phenotype may have significant implications for how we treat cancer. Yet, mature clinical studies definitively linking improved recurrence free survival to tissue egress of functional T_{RM} cells that can detect and eliminate residual or circulating cancer cells following ICB in neoadjuvant or induction studies in patients with newly diagnosed cancer are still needed. Investigation into the additional contribution of therapeutically inhibiting TGF-β or other environmental cues that promote T_{RM} cell differentiation to tissue egress and enhanced systemic antitumor immunity is specifically important because of the roles that TGF-β signaling also plays in tumorigenesis. Early in tumor progression, TGF-β inhibits epithelial cell proliferation, mainly through cell cycle arrest and induction of

apoptosis. In late-stage cancers, accumulation of genomic alterations within the epithelial compartment often results in the loss of TGF-β-associated anti-proliferative signaling[142,143]. As a result, the tumor promoting and immunosuppressive properties of TGF-β dominate in established malignancies, making it an attractive therapeutic target to both directly inhibit tumor cell proliferation and survival as well as to enhance anti-tumor immunity. In this review, we mainly explored the role of TGF-β in the differentiation of tumor-resident CD8 T cells and how targeting TGF-β signaling could lead to the egress of tumor-reactive T cells from the tumor into circulation and the resulting enhanced systemic immunity. Considering this mechanism, TGF-β inhibition is rational in the neoadjuvant setting prior to surgical removal of the tumor. The decision to inhibit TGF-β in other setting such as relapsed or metastatic disease must consider other effects of TGF-β blockade on the tumor cell and immune compartments. What is clear, however, is that failing to ‘use the tumor as a vaccine’ and promote systemic antitumor immunity through therapeutic reversal of tumor sequestration of tumor specific T cells prior to definitive treatment is failing to offer patients with newly diagnosed cancers a better chance at long term recurrence free survival.

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Highlights

- Tissue resident T cells (T_{RM}) express adhesion molecules and embed within tissues
- T_{RM} promotion in tumors leads to sequestration of T cells out of circulation
- Definitive surgery or tumor ablation may remove most tumor-specific T cells
- Neoadjuvant immunotherapy promotes egress of T_{RM} from tumors into circulation
- This effect may underlie the clinical benefit observed with neoadjuvant immunotherapy

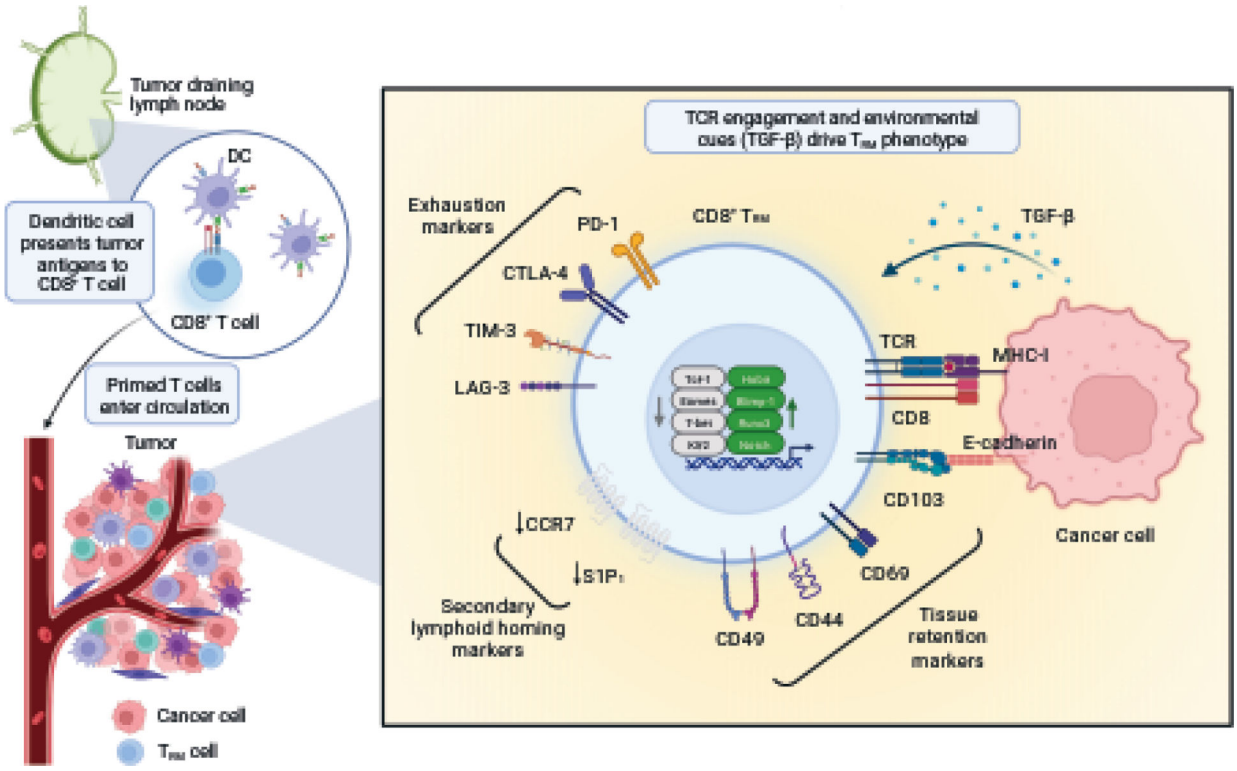

Figure 1: Mechanisms of development and maintenance of T_{RM} cells.

Tissue-specific dendritic cells (DCs) migrate to the draining lymph nodes (dLN) where they present antigens to naïve T cells. Once primed, these T cells have the capacity to become $CD8^+$ T_{RM} precursors and migrate to the injured tissue, following a chemotactic gradient. In the tissue, exposure to transforming growth factor beta (TGF-β) initiates the resident memory program, namely by driving the expression of the integrin alpha E (ITGAE/CD103) that binds to E-cadherin expressed by the tissue, enforcing retention. TGF-β is also important in driving the general transcriptional profile of T_{RM} cells, which requires the expression of Hobit, Blimp-1, Runx3 and Notch and downregulation of Tcf-1, Eomes, T-bet and Klf2. T_{RM} cells are often characterized by the expression of immune checkpoint receptors associated with T cell exhaustion such as Lag-3, TIM-3, CTLA-4, and PD-1.

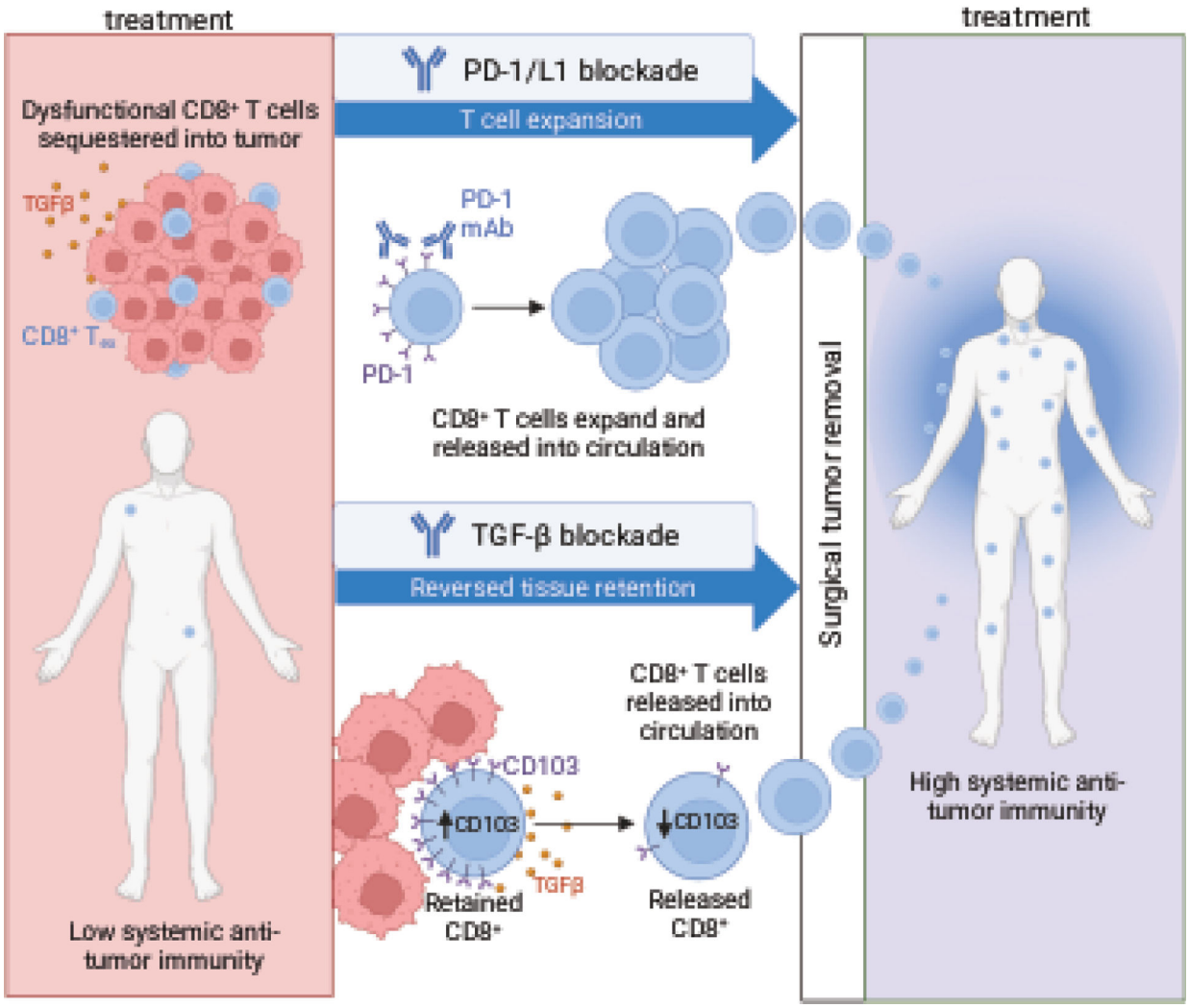

Figure 2: Neoadjuvant therapy as a strategy to induce recirculation of T_{RM}-like cells and systemic immunity against cancer.

Through expression of tissue resident markers such as CD103, exhausted, dysfunctional $CD8^+$ T cells reside in tumor tissue. PD-1 targeting immune checkpoint blockade with or without TGF- β blockade enhance egress of $CD8^+$ T cells out of the tumor and into circulation prior to surgical removal of the tumor. This treatment result may increase the systemic anti-tumor immunity of the patient and improve recurrence free survival.