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Tissue-Resident Memory-Like T Cells in Tumor Immunity: Clinical Implications

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Abstract

Tissue-resident memory (T_{RM}) T cells are distinct population of non-circulating lymphocytes that play an important role in mediating regional immunity. T_{RM} -like cells have now been identified as a component of tumor-infiltrating lymphocytes in several human tumors and correlate with outcome and response to immunotherapy. T_{RM} cells have also been shown to mediate anti-tumor immunity in murine models. Biology of T_{RM} cells has several implications for clinical cancer immunotherapy. Here we discuss newer insights into the biology of T_{RM} T cells and discuss their implications for understanding the heterogeneity of immune microenvironment in tumors as well as improving the efficacy of cancer vaccines, immune-checkpoint blockade and adoptive cellular therapies in the clinic.

Immune system consists of both innate as well as adaptive components with potent capacity to control tumors. Success of therapies that block inhibitory immune checkpoints on T cells, as well as therapies that redirect T cells (such as via chimeric-antigen receptors (CAR), or bispecific antibodies), have transformed clinical oncology and placed T cells at the center of immune-mediated approaches to battle cancer¹. An important aspect of T cell immunity is the property of immunologic memory, which is essential for long term protection². Tissue-resident memory (T_{RM}) T cells are a phenotypically and transcriptionally distinct population of non-recirculating memory T cells that reside within non-lymphoid tissue and provide regional protection against pathogens and tumors in several models^{3,4}. In this review, we discuss emerging insights about the biology of these cells in the setting of cancer with a particular focus on human T_{RM} cells and the implications of recent studies on T_{RM} s for harnessing tumor immunity in the clinic.

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Lessons from Mice:

T_{RM} cells have been classically identified as non-recirculating T cells that reside and renew within tissues and do not equilibrate with circulating T cell pool. In mice, T_{RM} compartment has been studied using various approaches including parabiosis^{5,6}, transplantation^{7,8}, intravascular labeling^{9,10} and targeted antibody-mediated T cell depletion⁴. While the majority of studies have focused on CD8+ T_{RM} cells, the presence of CD4+ T_{RM} cells has also been characterized in both humans^{11,12} and mice¹³. In contrast to circulating T cells (including effector memory and central memory T cells) that may transit through tissue but return to blood or secondary lymphoid organs, T_{RM} T cells do not circulate through these compartments⁴. CD8+ T_{RM} cells in several epithelial tissues express CD69 and CD103. CD69 is expressed early during T_{RM} development and serves to maintain tissue retention via downregulating egress signals such as S1PR1 (sphingosine 1-phosphate receptor-1)¹⁴. CD103 is regulated by cytokine signals such as TGF-beta and helps maintain interactions with epithelial markers such as E-cadherin¹⁵. T_{RM} cells lacking CD103 can however be detected in some tissues and phenotypic identification of these cells based on limited markers can therefore be challenging. Transcriptome signatures that distinguish T_{RM} cells from other counterparts have been published, but many of the genes in these signatures are not specific to T_{RM} cells and are also expressed in T cell subsets^{16–19}. It is increasingly apparent particularly with new single cell tools that T_{RM} cells exhibit functional and phenotypic heterogeneity, which may depend in part on the specific tissue studied. CD8+ T_{RM} cells develop early after activation from effector-like precursors wherein local tissue microenvironment drives resident fate. In some settings, cytokines such as IL15 and TGF-beta are important for T_{RM} generation²⁰. Expression of certain transcription factors such as Hobit¹⁶, Runx3²¹ and Nur-77 / NR4A1¹⁸ has been shown to be important for generation of T_{RM} cells. Antigen recognition within tissues was shown to be important for T_{RM} cells in neural tissue and models of HSV-1 infection in the lung, but less relevant in other settings^{22,23}. In the steady state, T_{RM} cells in many tissues can be maintained without ongoing replenishment from circulating precursors, although this may be required for T_{RM} cells in murine lung^{8,24}. In mouse skin and female reproductive tract, T_{RM} cells are able to proliferate locally upon activation, without being displaced by other cell types, but can also leave tissues to contribute to systemic immunity^{25–27}. It is increasingly appreciated that T_{RM} cells are indeed capable of contributing to the circulating memory pool and thereby providing an “outside-in” mechanism for protective immunity²⁸. T_{RM} cells may also be capable of retrograde migration to lymph nodes where they may contribute to long lived immune cells²⁹. These considerations are leading to proposals for new models for integrating T_{RM} cells into traditional T cell differentiation models, understanding the plasticity and interconversion between these compartments^{30,31}. It is notable that even in the studies wherein ex- T_{RM} cells reach lymphoid tissues or systemic circulation, they seem to maintain a stable epigenome and seem poised to preferentially home back to tissue of origin^{28,29}. Small proportions of T cells with T_{RM} signatures and phenotypes have been detected among circulating T cells in humans^{18,32}. A small subset of T_{RM} cells with dye efflux properties seem to be a quiescent subset of T cells in both humans and mice^{18,33}, with “label retention” properties similar to tissue stem cells, which may allow them to persist long term. Until recently, most of the data relating to protective effects of T_{RM} cells in mice

has been limited to pathogens^{8,22}. In several studies, T_{RM} cells provide superior protection against viral or bacterial pathogens in peripheral tissues^{6,8}. The underlying mechanisms involve direct effects as well as recruitment of other immune cells, although T_{RM} cells are able to mediate protection without the requirement of circulating effectors^{27,34}. As discussed below, T_{RM} cells are now also emerging as important players in mediating tumor immunity³⁵.

Evidence for human T_{RM} T cells

As experimental parabiosis is not feasible in the human setting, evidence for equivalent tissue-localized T cells in humans has been based on finding T cells that persist in tissues following organ transplantation or antibody-mediated depletion of circulating T cells. HLA-mismatched T_{RM} cells can persist long term in patients following lung and bowel transplants^{36–38}. Administration of anti-CD52 antibody (alemtuzumab) depletes circulating T cells without concurrent depletion of skin-resident T cells, illustrating their disequilibrium with circulating compartment^{39,40}. T cells with T_{RM} phenotype have been shown to be enriched in barrier tissues studied over several decades of life⁴¹. In humans, as in mice, T_{RM} cells have been characterized by the expression of markers such as CD69, CD103 (in some tissues), and downregulation of tissue egress or migration molecules such as S1PR1, KLF2, and L-selection⁴. The phenotype is often tissue-specific and also heterogenous within tissues, leading to functional differences with some subsets such as CD49a+ T_{RM} cells shown to express more interferon- γ ^{42,43}. Transcriptional profiles of human T_{RM} cells seem to resemble murine counterparts, but there are some differences. For example, Hobit is commonly expressed in murine T_{RM} cells wherein it plays an important functional role¹⁶, but its expression in human T_{RM} cells has been harder to detect¹¹.

Preclinical studies for anti-tumor potential of T_{RM} cells

Potential role for T_{RM} cells in tumor immunity first emerged from studies showing T_{RM} phenotype of T cells infiltrating human tumors^{44,45}, but their anti-tumor properties and role in immune surveillance has now been demonstrated in the context of murine models as well^{46,47}. Mice lacking molecules expressed on T_{RM} cells such as CD69 or CD103 are more susceptible to transplantable melanoma than wild-type mice^{46,47}. T_{RM} cells generated by vaccination mediate protection against tumor challenge^{48–50}. In a melanoma model, T_{RM} cells generated during tumorigenesis and prior to tumor challenge were able to inhibit tumor growth, supporting a role for T_{RM} cells in surveillance and equilibrium phase of cancer control by maintaining occult melanoma in check⁴⁷.

Mechanisms of anti-tumor effects of T_{RM} cells

The mechanisms by which T_{RM} cells mediate anti-tumor effects remain to be fully clarified and may differ in specific settings and tumor type. CD103 expressed on some T_{RM} cells may promote immunologic synapse by binding to E-cadherin on tumor cells^{51,52}. A major mechanism of T_{RM}-mediated control may be via non-cytotoxic mechanisms and mediated in part by cytokines such as TNF⁴⁷. In this regard, T_{RM} cells may act more as controllers than as killers, similar to their role in control of latent / persistent viruses such as HSV1, where T_{RM}-mediated immunity does not lead to complete virus eradication but can maintain viral control for the life of the host. T_{RM} cells may also engage other immune cells and enhance

tumor immunity via antigen spreading by activating DCs⁵³. CD8+ T_{RM}-like cells may also mediate or amplify tumor immunity both by secreting cytokines (e.g. interferon- γ) or chemokines (e.g. CCL3, XCL1) to enhance recruitment of monocytes, NK cells and XCR1+ cDC1 to tumor site⁵⁴.

Generation and maintenance of T_{RM} T cells within tumors:

Information about the generation of intra-tumoral T_{RM}-like T cells is more limited compared to that for virus-specific T cells. Subsets of intra-tumoral T cells in human tumors express Hobit, but its role in biology of human T_{RM}-like cells is not clear. Lineage tracing and single cell transcriptomic studies have identified subsets of circulating effector cells as precursors with greater potential for T_{RM} generation in tumor models^{55,56}. TGF β is abundant in many tumors and could regulate T_{RM} generation, consistent with its role in non-tumor setting. Studies have also suggested a role for other pathways such as IL15 in intestinal cancer⁵⁷ or Notch signaling in head/neck cancer⁵⁸. Other mechanisms that may be operative include T_{RM} associated metabolic pathways such as exogenous fatty acid uptake⁵⁹ in tumors such as melanoma and breast cancer known to be enriched for free fatty acids, and hypoxic environments common in several tumors. It has also been suggested that local activation by distinct subsets of dendritic cells, such as the newly described cDC3 cells may play an important role in stimulation of T_{RM} cells⁶⁰. Taken together, these data, derived mostly from mouse models, suggest that diverse tumor and tissue-dependent pathways may be involved in the generation and maintenance of T_{RM}-like T cells within tumors.

T_{RM}-like T cells in human tumors

It is now well recognized that tumors are commonly infiltrated by heterogeneous populations of lymphocytes that include both innate and adaptive immune cells. Several studies have now demonstrated that a proportion of tumor-infiltrating lymphocytes (TILs) in human tumors express surface markers (e.g. CD69) or molecular signatures consistent with tissue resident memory T cells^{44,45,58,61,62}. CD69 expression can in principle also be induced by cognate antigen stimulation, although the genomic signatures of T_{RM} cells in tumor tissues, when studied, is different from that in recently activated T cells. In this regard, at least some of the T_{RM} cells within tumor tissues may be similar to those in the setting of persistent viruses wherein the local antigenic stimulus is persistent. Whether the expression of T_{RM} markers by human T cells in tumor tissue is analogous to those in non-malignant tissue is an area of active investigation. Although tissue residence of human tumor-infiltrating T_{RM} cells can not be directly tested by classical methods such as parabiosis, studies in patients with metastatic cancer have shown that dominant T cell receptors of T_{RM} cells in individual metastatic lesions show very little overlap in spite of the fact that all metastatic lesions share a systemic circulation as with parabiotic mice⁴⁵. Nonetheless, due to these experimental limitations, we have referred to these cells as T_{RM}-like TILs (T_{RM} TILs).

While detection of T_{RM}-like TILs cells based on single markers such as CD69 is challenging, we suggest that concurrent evaluation of tissue-retention signatures (such as downregulation of S1PR1) provides more robust evaluation of these cells. It is notable, that

while CD103 is commonly utilized to detect T_{RM} cells in epithelial tumors, the expression of CD103 is tissue-dependent, and lacking for examples in T_{RM} cells in the bone marrow.

T_{RM} TILs have now been described in several human tumors including non-small cell lung cancer^{44,58}, breast^{63,64}, colorectal⁶⁵, melanoma^{45,66}, genitourinary⁶⁷, gynecologic cancers⁶⁸, glioma⁶¹ and myeloma⁶² and constitute nearly 25–75% of all TILs^{45,69}. The presence of TILs with T_{RM} phenotype may not be restricted to solid tumors, and T cells with such phenotype can also be detected within tumor tissue in hematologic tumors such as myeloma and its precursor states^{62,70,71}. Infiltration of tumors by TILs has been associated with improved survival in several tumor types⁷². However recent data suggest that the T_{RM} component of the TILs may be particularly relevant for predicting outcome^{58,66}. T_{RM} TILs have also been shown to exhibit strong effector and cytolytic function compared to non-T_{RM} TILs⁴⁴. As an example, CD39+ T_{RM}-TILs were shown to be enriched for tumor reactivity in several tumor types⁷³. It is important to note that while tumor-antigen-specific T cells have been claimed to be enriched within subsets of T_{RM} cells, not all of the T_{RM} cells within tumor tissue are tumor-specific. Both self-reactive as well as pathogen-reactive T_{RM} cells have been detected within tumors^{74,75}. Interestingly, studies have also suggested that activation of these “by-stander” T cells may mediate anti-tumor activity and therefore could in principle be repurposed for tumor therapy⁷⁵. Together, these studies have not only documented the presence of T_{RM}-like TILs in several tumors, but their strong correlation with clinical outcome also suggest that these are important components of protective tumor immunity. Recent application of single cell tools has characterized the heterogeneity of tumor-infiltrating lymphocytes including T_{RM} cells, that may impact their biology^{62,76}. Below, we discuss some aspects of T_{RM} biology that may impact clinical application of immunotherapy.

Non-uniform regional immunity and inter-lesional heterogeneity

It is increasingly appreciated that degree of T cell infiltration within tumors is associated with improved outcome, occasionally in the absence of detectable circulating tumor-specific T cells, which points to the importance of regional immunity in cancer. However, the degree to which this regional immunity remains localized to the tumor lesion or whether it has considerable systemic component has broad implications not just for measuring and harnessing immune responses in the clinic but also cancer biology in general. Dominant T cell receptors infiltrating individual metastatic lesions can differ considerably^{45,77,78}. In a recent study, it was shown that this inter-lesional heterogeneity in dominant T cell receptors (TCRs) is predominantly derived from the subset of T cells that express markers of T_{RM} cells⁴⁵. Importantly, this heterogeneity of T cell response exceeds the differences in mutations or predicted neoantigens in these lesions. As all metastatic lesions in any individual patient share the same systemic circulation, the concept that the T cells do not “equilibrate” in vivo in patients in spite of antigenic similarity between individual metastatic lesions is highly reminiscent of regional nature of immune responses due to T_{RM} cells in parabiotic mice. This concept in turn suggests that it is important to pay attention to the specific lesion biopsied in order to track changes in immune response following immune therapies. Inter-lesional differences in immune response may also impact genomic evolution of tumors at individual sites, as it may impact immune pressure that each lesion experiences,

particularly in view of emerging role of T_{RM} cells in the equilibrium phase of immune editing^{47,77,79}. This heterogeneity may also provide a potential explanation for several observations following immune therapies in the clinic. For example, it is well known that some patients achieve “mixed responses” following checkpoint blockade, with varying degree of regression in individual lesions⁸⁰. Along the same lines, regional nature of immune response may also provide an explanation for the observations in the clinic that disease progression at a single site may not equate to global loss of systemic tumor immunity and some of these patients have achieved durable responses following local control of the progressing lesion^{81,82}. It should be noted that while T_{RM} cells do not recirculate in steady state, it is possible that they are capable of in situ proliferation following activation and this may then primes them towards exiting tumor tissue and contribute to systemic immunity as has been shown in mouse models²⁵. Whether such biology occurs in clinically relevant settings needs to be studied.

T_{RM} cells as targets to improve cancer vaccines

The field of cancer vaccines is replete with examples wherein vaccine-induced systemic or circulating T cell responses do not correlate with protective immunity or tumor regressions in the clinic. Based on the considerations discussed earlier, it is tempting to speculate that an important missing link may be the inability of current vaccines to effectively enhance T_{RM} cells within tumors. Mucosal vaccination protocols that lead to greater generation of T_{RM} cells mediate greater protection than systemic vaccines against head and neck cancer or melanoma in murine models^{48,83,84}. Vaccine-induced T_{RM} cells have been shown to mediate anti-tumor effects in mice⁴⁸. At present, the degree to which current vaccines effectively induce tumor-infiltrating T_{RM} cells and how to optimize it requires further study. Regional administration of vaccine constructs or immune stimulatory agents to mediate in situ vaccination may be one way to achieve these goals and is undergoing evaluation.

Repeated boosting with heterologous viruses carrying cognate antigen can enhance T_{RM} cells within tissues and such approach could lead to enhanced tumor immunity⁸⁵. Another strategy that has been attempted involves a push and pull approach that combines initial priming to generate T_{RM} precursors and then pulling them into tumors via chemokine gradients⁸⁶. The nature of tumor-infiltrating T_{RM} cells induced by vaccines do not have to be tumor-specific in order to mediate tumor immunity. In a preclinical study, peptide injection targeting virus-specific T_{RM} cells led to effective tumor regression, particularly in combination with checkpoint blockade⁷⁵. While the importance of dendritic cells in generation of T cell responses is well appreciated, the nature of specific antigen-presenting cells or DC subsets that need to be targeted to induce T_{RM} T cells in situ needs greater clarity. In one study, engagement of CD1c+ DCs was shown to lead to induction of skin-homing T_{RM} cells⁸⁷. Induction of immune response following activation of T_{RM} cells may depend on engagement of Batf3-expressing CD141+ subset of DCs that are specialized for cross-presentation⁸⁸. Strategies to enhance targeting of DCs via DC-specific antibodies or nanoparticles are under active evaluation but will need to consider their capacity to enhance T_{RM} T cells within tumors^{89–91}.

T_{RM} cells as targets of immune checkpoint blockade

Blockade of immune checkpoints such as PD-1 has transformed immune therapy of human cancer. However, these checkpoints are expressed on only a subset of T cells within human tumors. Several studies have shown that T cells with T_{RM} phenotype and genomic signatures are the subset of tumor-infiltrating T cells with highest level of expression of inhibitory immune checkpoints within human tumors^{45,61}, raising the possibility that T_{RM} cells are an important target of immune checkpoint blockade, particularly those targeting PD-1. Blockade of PD-1 in vitro can enhance cytokine production by these T cells, supporting the possibility that these immune checkpoints serve to provide a restraint on T_{RM} function in situ⁹². Tumor immunity in melanoma can be associated with the development of vitiligo in some patients, which in turn is now recognized as associated with activation of skin-resident T_{RM} T cells^{42,93}. Presence of T cells with T_{RM} phenotype or T_{RM} signatures within human tumors has been correlated with improved survival following IC blockade^{58,66}. At present, it remains unclear whether the T_{RM} compartment within tumors undergoes proliferation within tumors *situ* to mediate anti-tumor effects, or whether recruitment of new T cells into tumors is needed to mediate effects of IC blockade (or combination thereof) and findings supportive of both possibilities have been described in preclinical models^{94–96}. Recent studies have also identified a subset of TCF1+ T cells termed as precursor exhausted or stem-like memory T cells that undergo proliferative boost following PD-1 blockade in mouse models of chronic LCMV infection⁹⁷. Such T cells have also been identified in human tumors, and in some small cohorts linked to outcome following checkpoint blockade as well⁹⁸. While TCF1+ cells within tumors do commonly express CD69 (a marker of T_{RM} cells), they are distinct from CD103+ T_{RM} cells which do not express TCF1. In preclinical models TCF1 was shown to inhibit CD103 and tissue residence⁹⁹. In a recent study of T cells infiltrating pediatric gliomas, TCF1+ T cells were found to be mostly perivascular in location, while CD103+ T cells were further away from the vessels and infiltrating the tumor tissue.¹⁰⁰ Further studies are needed to better understand the functional and spatial heterogeneity within the T_{RM}-like compartments and their role/contributions to effects of IC blockade.

T_{RM} cells as targets of adoptive cell therapies

The ability of adoptively transferred T cells to infiltrate into tumors and persist long term have emerged as essential characteristics for effective therapy. These features are also imprinted into the biology of T_{RM} cells. Adoptive transfer of tumor infiltrating lymphocytes, which contain a variable but high proportion of T_{RM} cells, has been shown to mediate tumor regression in patients with melanoma and renal cell cancer¹⁰¹. Indeed, among TILs, tumor-specific T cells were shown to express higher levels of PD-1, which is also a characteristic of T_{RM}-like TILs¹⁰². Activated T cells infiltrating murine tumors rapidly acquire large component of transcriptional program of T_{RM} cells^{103,104}. T cells with Hoechst dye exclusion phenotype, which also exhibit T_{RM}-like signatures, lead to greater tissue infiltration upon adoptive transfer¹⁸. Overexpression of residency promoting transcription factor Runx3 in T cells led to greater tissue infiltration of adoptive transferred T cells and enhanced anti-tumor effects of adoptive cell therapy²¹. Enhancing tumor or tissue infiltration may be particularly important in the setting of chimeric-antigen receptor (CAR)-T cell therapy for solid tumors, which have thus far been relatively unresponsive to such therapies¹⁰⁵. Several strategies are being considered to enhance the effectiveness of adoptive

cell therapies by engaging T_{RM} biology. This includes genetically reprogramming T cells to enhance T_{RM} signatures, or preselecting T cell substrates with greater potential for differentiation to T_{RM} cells, either isolating precursor T cells from tissues themselves or mobilizing T cells from tissues into circulation. One example of the latter strategy is the use of CXCR4/SDF1 antagonists to mobilize T cells from the bone marrow, which is analogous to stem cell mobilization currently used in stem cell transplantation¹⁸. Further studies are needed to better understand whether enhancing T_{RM}-like features in adoptively transferred T cells will lead to improved efficacy, particularly against solid tumors.

Summary:

Cells with phenotype and genomic signatures of tissue-resident memory T cells have been identified in several human tumors, wherein they correlate with outcome and response to immune therapy^{35,69}. Anti-tumor effects of these T cells have also been demonstrated in preclinical models. T_{RM} biology has profound implications for how to optimally engage and enhance tumor immunity in the clinic. However, several questions relating to their generation, heterogeneity, tissue residence, maintenance and anti-tumor effects remain to be fully characterized. Further studies should help to clarify the biology of these T cells, particularly in human tumors, and may lead to novel approaches for cancer immunotherapy.

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