Introduction

The lungs are constantly exposed to pathogens throughout life and continually need to develop and maintain immunity against infection. T cell immunity is provided by central memory T cells (T_{CM}), effector memory T cells (T_{EM}) and resident memory T cells (T_{RM}) to enable rapid responses against re-infection. Each memory cell type has a distinct location: T_{CM} are mostly present in secondary lymphoid organs and the circulation, T_{EM} patrol the blood, transiently entering peripheral organs, and T_{RM} permanently reside in most tissues such as the lung, gut, skin, brain and liver (1-4). T_{RM} form a defensive barrier against viral and bacterial infections and have also emerged as an important population in regulating anti-tumor immunity (5,6). High numbers of tumor infiltrating lymphocytes (TILs) that display a CD103^{+} T_{RM}-like phenotype in carcinomas have been associated with improved survival in multiple solid cancers (7-9). These T_{RM}^{+} TILs likely play...
Table 1 Summary table depicting distinct characteristics of healthy lung T<sub>RM</sub> and T<sub>RM</sub>-like tumor-infiltrating lymphocytes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy lung T&lt;sub&gt;RM&lt;/sub&gt;</th>
<th>T&lt;sub&gt;RM&lt;/sub&gt;-like tumor infiltrating lymphocytes</th>
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<tr>
<td>CD39 is not expressed by healthy lung T&lt;sub&gt;RM&lt;/sub&gt;</td>
<td>CD39 marks tumor neoantigen-specific T&lt;sub&gt;RM&lt;/sub&gt;-like TILs</td>
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<tr>
<td>Rapid response to repeated infection</td>
<td>High number of T&lt;sub&gt;RM&lt;/sub&gt;-like TILs associated with better cancer survival</td>
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<tr>
<td>Relatively quiescent</td>
<td>Proliferative</td>
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<td>Poised for cytotoxicity: RNA encoding pro-inflammatory cytokine (IFN-γ, IL-17, IL-2, IL-10 and TNF-α) and cytotoxic mediators (granzyme B, perforin)</td>
<td>Strong cytotoxic activity expressing high levels of granzyme B, perforin, IFN-γ, TNF-α</td>
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<td>Express co-inhibitory molecules PD1, LAG3, TIM3</td>
<td>Express higher levels of co-inhibitory molecules PD1, LAG3, TIM3</td>
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<td>Broad TCR repertoire</td>
<td>Clonal expansion of T&lt;sub&gt;RM&lt;/sub&gt;-like TILs with a narrow TCR repertoire against tumor-specific neoantigens</td>
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Identification and phenotype of lung T<sub>RM</sub> in health and cancer

Human T<sub>RM</sub> were first identified following HLA-mismatched transplantation (14) and depletion of circulating memory T cells with anti-CD52 antibody studies (Alemtuzumab) (15), which demonstrated a population of tissue-resident cells in disequilibrium with the blood. These initial studies established CD69 and the integrin CD103 to be canonical markers associated with T<sub>RM</sub> (14,15). Further studies have elucidated markers specific to T<sub>RM</sub> and factors responsible for their maintenance [reviewed in (16,17)]. Like T<sub>RM</sub>, T<sub>RM</sub> express the memory marker CD45RO, and do not express CD45RA, a marker of naïve T cells and terminally differentiated effector memory T cells (T<sub>EMRA</sub>), nor the lymph node homing marker CCR7 (18). T<sub>RM</sub> can be distinguished based on their expression of CD69, CD103<sup>+</sup>- and CD49a<sup>+</sup>, although T<sub>RM</sub> that do not express these markers are likely to exist, as is found in mice (19). CD69 is a transmembrane C-Type lectin protein that prevents egress of T cell from tissues by interfering with the activity of the receptor for the bioactive lipid sphingosine-1 phosphate (20). CD103, or integrin alpha E (ITGAE) is induced by TCR engagement in the presence of transforming growth factor beta (TGF-β) (21) and forms a complex with integrin beta 7 (ITGB7). This complex binds to e-cadherin present on epithelial cells to promote the intra-epithelial retention of CD103<sup>+</sup> T<sub>RM</sub> (22). The majority of CD8<sup>+</sup> mouse and human lung T<sub>RM</sub> express CD103, but CD103 is only expressed in less than a quarter of human CD4<sup>+</sup> T<sub>RM</sub> and absent on mouse CD4<sup>+</sup> T<sub>RM</sub> (19,23). CD49a [integrin alpha 1 (ITGA1)] and CD11a [integrin alpha L (ITGAL)] are expressed by CD8<sup>+</sup> and CD4<sup>+</sup> T<sub>RM</sub> although the expression of CD11a appears restricted to alveolar T<sub>RM</sub> (23-28). These
integrins are involved in cellular adhesion and costimulatory signaling, and CD11a is also required for CD8+ T cell entry in the lung parenchyma (29).

While CD103 and CD69 are commonly used markers of T<sub>RM</sub> in healthy tissues, relying on these markers to identify T<sub>RM</sub> in TILs may be problematic. The expression of CD103 can be induced on circulating CD8<sup>+</sup> T cells in the presence of TGF-β (30) which is secreted in the tumor microenvironment. CD69 is transiently expressed in response to antigen or inflammation, such that CD69-expressing T cells in tissues may be activated and transiting through the tissue, but not resident (31). Nevertheless, multiple studies have now shown that TILs in NSCLC and other solid tumors display a phenotype reminiscent of T<sub>RM</sub>, describing them as T<sub>RM</sub>-like cells (5,6,8,32). In lung tumors, not all CD69<sup>+</sup>CD8<sup>+</sup> or CD4<sup>+</sup> TILs express CD103 (6). While the number of CD69<sup>+</sup>CD103<sup>-</sup>CD8<sup>+</sup> T cells increases in lung tumors compared with normal lung, CD69<sup>+</sup>CD103<sup>-</sup>CD4<sup>+</sup> are more prevalent in the tumor than in the normal lung, and are more abundant than CD69<sup>+</sup>CD103<sup>+</sup>CD4<sup>+</sup> TILs (6). The T<sub>RM</sub> pool in TILs therefore consists of diverse subsets of cells, with varying levels of expression of CD69 and CD103. CXCR6 and CD49a have also been shown to define T<sub>RM</sub>-like TILs being expressed in both CD69<sup>+</sup>CD103<sup>+</sup>CD4<sup>+</sup> and CD69<sup>+</sup>CD103<sup>-</sup>CD8<sup>+</sup> TILs (6).

Insights into markers of tumor-specific T<sub>RM</sub>-like cells has also come from the analysis of markers of T<sub>RM</sub> in chronic infectious diseases. CD39, a marker of exhausted T cells in patients with chronic viral infection was found to be expressed in tumor infiltrating CD103<sup>+</sup>CD8<sup>+</sup> TILs in head and neck squamous cell carcinoma, lung, melanoma, ovarian, and colorectal cancer (32). CD39 is highly expressed in CD103<sup>+</sup>CD8<sup>+</sup> TILs compared with CD103<sup>-</sup>CD8<sup>+</sup> TILs in early stage NSCLC tumors (5). CD39<sup>+</sup>CD103<sup>-</sup>CD8<sup>+</sup> T cells were also detected in metastatic lymph nodes, but not in non-tumor involved lymph node or the circulating blood, suggesting that CD39 is a marker of tumor-specific T<sub>RM</sub>-like cells (32). CD39 is a cell surface ectonucleotidase that dephosphorylates ATP to AMP. Excess ATP can be toxic for cells, suggesting that CD39 expression by CD103<sup>+</sup>CD8<sup>+</sup> cells may be a way to protect T<sub>RM</sub>-like TILs from ATP-induced cell death. CD39 may prove to be a critical marker to distinguish tumor neoantigen-specific T<sub>RM</sub>-like TILs from other antigen-specific T<sub>RM</sub>. Simoni et al. observed that in lung tumor and colorectal cancer, only CD39<sup>+</sup>CD8<sup>+</sup> TILs and not CD39<sup>+</sup>CD8<sup>+</sup> TILs had undergone neoantigen-driven clonal expansion (12). Analysis of 40 human lung cancer samples by mass cytometry revealed that a large portion of TILs were bystander CD8<sup>+</sup> TILs that express CD103 and CD69 but did not express cancer-related epitopes (12). These bystander CD8<sup>+</sup> T<sub>RM</sub>-like TILs express coinhibitory molecules such as PD1, but do not express CD39. CD38, another ectonucleotidase that also regulates adenosine signaling, was found highly expressed in NSCLC CD103<sup>+</sup> TILs further suggesting that regulation of the adenosine pathway may be an important mechanism for tumor-specific T<sub>RM</sub> (5).

Further insight in the heterogeneity and distinguishing features of cancer T<sub>RM</sub>-like TILs compared to healthy tissue T<sub>RM</sub> will come from the use of novel single cell technologies including single cell RNA sequencing (scRNAseq), cytometry-based assays including mass cytometry (CyTOF), CITE-seq, and multi-parametric immunostaining technics. Single cell RNAseq analysis of lung CD103<sup>+</sup> TILs compared with non-malignant tissue CD103<sup>+</sup> T cells has revealed greater activation of these T<sub>RM</sub>-like cells in NSCLCs, where the protein expression of additional cell surface markers could further clarify the heterogeneity and tumor-specificity of T<sub>RM</sub>-like TILs (33). High parameter mass cytometry experiments (34), or CITE-seq that takes advantage of DNA-barcoded antibodies combined with scRNA sequencing (35) constitutes novel technologies to explore distinct features of T<sub>RM</sub> in cancer and healthy tissue from the same organ. Multi-parameter immunostaining methodologies in tissue would also complement these approaches to provide in depth information on the spatial organization of these cell types (36).

**Localization and regulation of lung T<sub>RM</sub>**

The location and turnover of lung T<sub>RM</sub> is tightly controlled to ensure rapid defense against infection while preserving tissue integrity. Lung T<sub>RM</sub> are localized in two different compartments in the human and mouse lung: the lung parenchyma or alveolar region, and the airsacs (bronchi and bronchioles) (24,28,37-40). Studies analyzing the precise localization of T<sub>RM</sub> have been conducted in the mouse lung following influenza infection (41,42). A month after flu infection, CD4<sup>+</sup>T<sub>RM</sub> were found clustered in a niche surrounding the mouse airsacs, in proximity to the primary site of reinfection, consistent with their helper T cell role (28). In contrast, CD8<sup>+</sup> T<sub>RM</sub> did not form clusters and were detected within the epithelial repair region in the parenchyma and peribronchial area (25) (Figure 1A). In the human lung, CD4<sup>+</sup> and CD8<sup>+</sup> T<sub>RM</sub> are detected in both the
parenchyma and the airways (38). The 3D localization of T_{RM} within bronchiolar and alveolar regions is still unclear, and how these locations may facilitate ready exposure to inhaled memorized antigens remains to be elucidated.

To maintain cellular homeostasis and prevent unnecessary immunopathology, cell death and proliferation of lung T_{RM} are tightly regulated (37,43). Particularly, mouse airways T_{RM} have a relatively short half-life of 14 days (39,40,43). Mouse studies have shown that alveolar CD8^{+} T_{RM} will only form after exposure to an antigen within the lung and are maintained through a slow regenerative turnover in the alveoli (24,44). Alveolar CD8^{+} T_{RM} constantly replenish the pool of short-lived airways CD8^{+} T_{RM} by migrating to the front line to respond to re-infection events (24) (Figure 1A). CXCL16 expressed by the airway epithelium appears to be the most prevalent chemokine responsible for the migration of CD11a^{+}CXCR6^{+}CD8^{+} T_{RM} from the parenchyma to the airways where the expression of CD11a and CXCR6 is then downregulated (23,24,40,45-47). Interestingly, there are some differences in the level of expression of CD103 and CD69 in T_{RM} present in human lung airways or the parenchyma where the airways have more than a two-fold increase in the proportion of CD69^{+}CD103^{+} expressing CD8^{+} and CD4^{+} T cells compared with the alveolar parenchyma that has a higher proportion of CD69^{+}CD103^{+} cells (38). These results are reminiscent to what is observed in the human skin where the epidermis contains CD69^{+}CD103^{+} CD4 and CD8 T cells, whereas the CD69^{+}CD103^{+} subset is more prevalent in the dermis for both CD4 and CD8 T_{RM} (48). In the skin CD69^{+}CD103^{+} T_{RM} express more effector cytokines such as IFN-γ and TNF-α than CD69^{+}CD103^{+} T_{RM} (48). It remains to be evaluated whether the same is true in the different subpopulations of lung T_{RM}.

Molecular mechanisms controlling tissue residency of lung T_{RM} appear to be distinct from other tissue-specific T_{RM}. Mouse studies have shown that Hobit, Blimp1 and Runx3 are important mediators of tissue residency in the small intestine, liver, kidney and skin, by directly down-regulating the expression of tissue egress receptor CCR7 and S1PR1 (49-51). However, detailed investigation of transcriptional programs regulating mouse lung CD8^{+} T_{RM} showed that Blimp1, but not Hobit, was required for their formation following influenza virus infection (52). In human lung, RUNX3 and HOBIT may be involved in the generation and/or maintenance of CD8^{+} T_{RM} (38,50), although the expression of HOBIT appears lower in human lung T_{RM} than mouse T_{RM} (23), suggesting RUNX3 may be a common regulator of lung T_{RM} in both species. Indeed, human and mouse T_{RM} share a core transcriptional signature associated with RUNX3 expression (50). Runx3 also plays an important role in regulating TILs in a mouse...
model of melanoma, where Runx3-deficient T-cells fail to accumulate in the tumor, resulting in increased tumor growth. Conversely, overexpression of Runx3 increased the recruitment of CD8+ T cells to the tumor and these TILs expressed a transcriptomic signature of tissue-residency (50). Further investigation will be necessary to specifically delineate the role of these distinct transcription factors in regulating T\textsubscript{RM} in healthy lung and lung tumors.

In early stage NSCLC, infiltration of CD103\textsuperscript{+}CD8\textsuperscript{+} T\textsubscript{RM}-like TILs in the tumors correlated with better patient survival (8). Interestingly, while a large proportion of these T\textsubscript{RM}-like cells resided in the tumor stroma, high infiltration of T\textsubscript{RM}-like TILs within the tumor was associated with an increase in the number of all TILs, irrelevant of the histological subtypes of NSCLC (Figure 1B). Those tumor-penetrating T\textsubscript{RM}-like cells were more frequently observed in patients with a history of cigarette-smoking and were associated with better outcome (8). This observation in lung cancer was similar to endometrial adenocarcinoma where CD103\textsuperscript{+}CD8\textsuperscript{+} T cells were found in the carcinoma region but not in the stromal region, consistent with the role of CD103 in homing to epithelial cells (53). These studies highlight the importance of the spatial organization of the tumor microenvironment and suggest that in situ analysis will be critical to understand the role played by T\textsubscript{RM}-like TILs in anti-tumor immunity.

In cancer progression, tumor cells utilize high levels of oxygen and nutrients leading to an aberrant metabolic state within the tumor-microenvironment (54). This nutrient deprivation may limit the lifespan and effector functions of lung T\textsubscript{RM} (37) suggesting that the function of T\textsubscript{RM}-like TILs may also be impacted. Whether this nutrient-deprived environment limits the survival and function of T\textsubscript{RM}-like TILs or drives a reprogramming of their metabolic state promoting their survival and activity remains to be investigated.

**Lung T\textsubscript{RM} function in health and cancer**

In the healthy lung, T\textsubscript{RM} express a gene signature significantly different to peripheral blood circulating T cells, expressing genes encoding for effector molecules but also inhibitory regulators, indicating that these cells are poised for prompt response to infection, while maintaining immune tolerance (55). To rapidly recognize and respond to a large spectrum of invading pathogens, lung T\textsubscript{RM} express a large repertoire of TCR (26), with a higher TCR clonal diversity for CD4\textsuperscript{+} T\textsubscript{RM} compared with CD8\textsuperscript{+} T\textsubscript{RM} (49). T\textsubscript{RM} act rapidly against pathogens due to their high expression of mRNAs encoding pro-inflammatory cytokine (IFN-\gamma, IL-17, IL-2, IL-10 and TNF-\alpha) and cytotoxic mediators (granzyme B, perforin) which would presumably prevent delays required by transcription (23,26,37,38,49).

Similarly, T\textsubscript{RM}-like TILs are primed for cytotoxic activity. The interaction of CD103 with tumor cells through e-cadherin triggers lytic granule polarization and exocytosis, promoting anti-tumor cytotoxicity (30,56). Classification of early stage NSCLC tumors based on TIL expression of CD103 showed that in TIL-CD103\textsuperscript{hi} tumors, TILs expressed higher levels of genes associated with proliferation (Ki67, cell cycle genes) and cytotoxicity (granzyme B, perforin, IFN-\gamma) compared with TIL-CD103\textsuperscript{lo} tumors (5) (Figure 1B). Contrary to normal lung T\textsubscript{RM} that have a relatively quiescent phenotype (57,58), CD103\textsuperscript{+} TILs were shown to be more proliferative than CD103\textsuperscript{+} TILs (32,33). When CD103\textsuperscript{+}CD8\textsuperscript{+} cells were cultured in vitro in the presence of recombinant IL-2, cytotoxic degranulation was much more prominent in CD103\textsuperscript{+} cells compared with CD103\textsuperscript{+} cells isolated from the same tumor, as measured by granzyme B and CD107a expression (8). Further subdividing CD103\textsuperscript{+} cells with CD39\textsuperscript{-} showed that CD8\textsuperscript{+}CD39\textsuperscript{-}CD103\textsuperscript{+} could kill autologous tumor cells in an in vitro co-culture assay three-times more efficiently than CD8\textsuperscript{+}CD3\textsuperscript{+}CD39\textsuperscript{-} cells in an MHC Class I-dependent manner, indicating that CD39 is an important marker to select for cytotoxic tumor-specific T\textsubscript{RM} like TILs (32).

IFN-\gamma produced by T\textsubscript{RM} has been shown to increase the recruitment of circulating T cells to potentiate robust immune response to pathogens in infected tissue. IFN-\gamma stimulates chemokine production by epithelial cells and increases the expression of adhesion molecules by the vasculature resulting in higher T cell infiltration (59,60). Similarly, high production of IFN-\gamma by tumor-specific T\textsubscript{RM}-like cells may play a role in the recruitment of non-exhausted circulating T cells to the tumor. CD103\textsuperscript{+}CD4\textsuperscript{+} TILs were found to express the highest levels of TNF-\alpha and IFN-\gamma upon CD3/CD28 stimulation compared with CD103\textsuperscript{+}CD8\textsuperscript{+} TILs or their lung T\textsubscript{RM} counterparts (6). These cytokines may contribute to the recruitment of functional T cells to the tumor site (Figure 2A). Indeed, Wu et al. recently showed that recruitment of peripheral T cells may be an important factor in response to immune checkpoint blockade (ICB) (13). The authors combined scTCR-sequencing and scRNA sequencing of T cells in tumors, unaffected adjacent tissue and blood samples and showed an expansion of CD8\textsuperscript{+} T cell clones in the blood.
that were also detected in the unaffected and tumor tissue. These data offer a novel paradigm in our understanding of anti-tumor immunity and T<sub>RM</sub> biology, where CD103<sup>+</sup>CD4<sup>+</sup> tumor T<sub>RM</sub>-like cells may mediate recruitment of non-exhausted peripheral CD8<sup>+</sup> T cells to the tumor site. It remains to be seen how ICB act upon these CD4<sup>+</sup>T<sub>RM</sub>-like TILs, in parallel to reverting to a T cell exhaustion phenotype in CD8<sup>+</sup> TILs.

**Implications for therapy**

Therapies that activate the anti-tumor response of cytotoxic T cells have shown great promises in the management of lung cancer patients. However, there is still a wide disparity in responses to these checkpoint immunotherapies, where only 20% of lung cancer patients show response with different degrees of duration (61,62). The mechanisms behind a lack of response are still unclear, but recognition of a tumor-specific neoantigen by TILs is necessary for T cell mediated tumor cell destruction (63,64). Lung cancer-specific T<sub>RM</sub> are ideally placed as targets for immunotherapy which aims to enhance tumor immunosurveillance. Their rapid response upon re-exposure to antigen compared to circulating memory cells, their residency within the lung and their close contact with epithelial cells at risk of malignant transformation ensures their molecular features...
and spatial environment are primed for tumor control. Although neoantigen-reactive T cells can be detected in the circulation (65), it is still unknown if subsets of neoantigen-specific T cells become resident in the lung upon recognition of tumor neoantigens, likely due to the unsuitability of surface markers in tumors and the great heterogeneity of patients possessing bona fide tumor-reactive T cells (66). Approaches to target cancer-specific T RM for lung cancer treatment center around three major strategies: targeting existing cancer-specific T RM where they counteract the expression of activation molecules to limit inflammation-induced tissue damage and ensure immune tolerance (23,55). Compared with their normal lung counterparts, tumor-infiltrating T RM-like cells express higher levels of these co-inhibitory molecules. CD8^+CD103^+ Tumor T RM-like TILs express higher levels of TIM3, LAG3 and PD1 than CD8^+CD103^- TILs indicating that T RM-like TILs are the likely targets of immune checkpoint inhibitors (5,8,32,33) (Figure 2B). Although patients with TIL-CD103^hi lung tumors have a better overall survival outcome (5), this has not been linked to response to specific therapeutic strategies, including ICB. Exploring the exact balance of expression of co-inhibitory molecules on tumor-specific T RM-like cells and bystander T RM-like TILs will be necessary to evaluate these correlations. Nonetheless, in vitro studies showed that anti-PD1 or anti-PDL1 treatment was necessary to induce autologous tumor cell lysis by TILs and this effect was blocked in the presence of anti-CD103 antibody, indicating the critical role of CD103^+ cells in restoring anti-tumor immunity upon ICB treatment (8). It is likely that current ICB therapies are effective both upon cancer-specific T RM and also by inducing the recruitment of T cells from the periphery (5,8,13,32,68). Other immune checkpoints highly expressed by T RM-like TILs are under investigation in clinical trials, including TIM3 and LAG3 (69), which may be effective under similar mechanisms to current ICBs. Consistently, CD103^+ TILs in patients responding to anti-PD1 therapy expressed higher level of TIM3 than non-responders, indicating that inhibiting TIM3 may provide an additional therapeutic approach for tumors with primary or acquired resistance to anti-PD1 (33). Other sophisticated strategies include adoptive T cell therapy, where neoantigen-specific T cells are isolated and expanded from circulating T cells before re-infusion into the patient (70). A remaining question in the field is how long-term residency might be induced in cancer-specific T RM after successful immunotherapy for long term cancer immune-surveillance and control.

Recent studies have revealed a preponderance of bystander T RM within lung TILs that are reactive to unrelated epitopes (12). These cells are characterized by their lower expression of immune checkpoints compared to cancer-specific T RM-like TILs, yet it is tempting to speculate they may still contribute to current ICB sensitivity by producing effector cytokines to support cancer-specific T RM-like TILs or peripheral recruitment of effector T cells. In contrast, bystander lung and other organ T RM could also contribute to immune-related adverse events (irAEs), common in patients who are sensitive to ICB (71). IrAEs include pneumonitis, dermatologic, gastrointestinal, endocrine and hepatic inflammatory events, indicating that ICBs induce augmentation of systemic immunity. Whether these effects are mediated differentially through circulating immune cells and/or tissue-specific T RM remains to be explored. Use of genetically engineered mouse models will help understand the role of bystander and tumor-specific T RM-like TILs in mediating anti-tumor immunity, and to determine how this response is accentuated by ICB. Tracing of circulating T-cells and their recruitment to the tumor site may also provide insights into the effect of ICB and T RM-like TILs in the recruitment of T cells from the circulation. Analysis of the phenotype and TCR repertoire of T-cell populations in broncho-alveolar lavage fluid of patients who have developed pneumonitis as irAEs in response to ICB will also provide some clues on the mechanisms participating in the toxicity associated with ICB.

Tumor immunogenicity is necessary to induce an immune response. Immune escape mechanisms developed by tumor cells include loss of heterozygosity in major histocompatibility molecules I/II responsible for antigen presentation or reduced expression of neoantigens that can be recognized by T cell clones (72,73). The vast heterogeneity in the TCR repertoire detected in early stage tumors correlates with the genetic heterogeneity of tumor cells and diversity in predicted neoantigens (74). However, best responses to ICB appear to come from T cells responding to neoantigens that are universally present in every tumor clone (75). It is tempting to speculate that
the TILs recognizing a common neoantigen may have a T\textsubscript{RM}-like phenotype, due to their tumor-retention and persistence in the tissue. Indeed, TCR sequencing of CD103\textsuperscript{+} and CD103\textsuperscript{-} lung cancer TILs demonstrated a much narrower TCR repertoire of CD103\textsuperscript{+} TILs compared with CD103\textsuperscript{-} TILs, indicating a clonal expansion of T\textsubscript{RM}-like TILs against a restricted number of tumor-specific neoantigens (33). Validating this observation could have significant therapeutic implications, notably to permit the use of compounds activating co-stimulatory molecules on T cells. Such strategies include antibodies targeting 41BB, OX40, CD27 and ICOS, for which progress in the clinic has been hampered by both immune side-effects and complex overlapping roles of these molecules in other tumor-infiltrating immune cells (76-78). However, activating these co-stimulatory molecules specifically within T\textsubscript{RM}-like TILs may circumvent such issues. Other interventions to increase immunogenicity of tumors include oncolytic viruses in small cell lung cancer (79), dendritic cell vaccines, targeting myeloid-derived suppressor cells, chemotherapy and radiotherapy [reviewed in (80)]. The ability to induce residency of tumor-reactive T cells in these techniques should also be explored.

Conclusions

Tumor-specific T\textsubscript{RM}-like cells could play an important role in early stage and advanced disease. T cell recognition of neoantigens and subsequent residency of T\textsubscript{RM}-like TILs may help to prevent tumor relapse after successful treatment, and in late tumor evolution, T\textsubscript{RM}-like TILs recognition of clonal neoantigens could prevent further metastatic dissemination (75). An emerging challenge in these strategies is immune evasion developed by tumors, including loss of MHC Class I expression and ability to present antigens. Further research into the mechanisms inducing tumor residency and immune evasion by tumors will enable personalized medicine for the immunotherapy era.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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