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Transcriptional programming of tissue-resident memory CD8+ T cells

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Abstract

Tissue-resident memory $CD8^+$ T cells (T_{RM}) are localized in non-lymphoid tissues throughout the body where they mediate long-lived protective immunity at common sites of pathogen exposure. As the signals controlling T_{RM} differentiation are uncovered, it is becoming apparent that the dynamic activities of numerous transcription factors are intricately involved in T_{RM} formation. Here, we highlight known transcriptional regulators of T_{RM} differentiation and discuss how understanding the transcriptional programming of $CD8^+$ T cell residency in non-lymphoid tissues can be leveraged to prevent or treat disease.

Introduction: T_{RM} as a distinct memory $CD8^+$ T cell subset

$CD8^+$ T cells are critical for rapid eradication of intracellular pathogens. Following viral or bacterial clearance, the majority of the effector $CD8^+$ T cell population undergoes contraction while a small subset persists indefinitely as memory T cells, mediating durable protective immunity. Memory $CD8^+$ T cells can be broadly segregated into three distinct subsets: central memory (T_{CM}), effector memory (T_{EM}), and tissue-resident memory (T_{RM}) cells [1–4]. T_{CM} and T_{EM} populations are predominantly located in the blood and secondary lymphoid organs [4–7], although T_{EM} and T_{CM} can exhibit the capacity to survey non-lymphoid tissues (NLTs) [3]. T_{RM} are generally defined as memory $CD8^+$ T cells that permanently reside in NLTs without egress [3,8–10]; however, lymphoid tissues may also harbor non-circulating memory subsets as well [11–13]. While effective memory responses likely require the integrated activities of all three memory $CD8^+$ T cell subsets [14,15], T_{RM} exhibit sentinel immune surveillance activity and are critical in the earliest phases of secondary immune responses [10,15,16]. T_{RM} recognizing cognate antigen rapidly induce inflammatory responses, proliferate *in situ* [17,18], and trigger the trafficking of diverse immune cell types to the site of infection [15,16]. Infection-induced-T_{RM} have been identified in both barrier (e.g. skin, lung, intestine) and non-barrier (e.g. kidney, liver, brain) sites, and the protective activities of T_{RM} have been validated in numerous infection models including HSV [19–21], vaccinia [9,22–24], LCMV [25], influenza [26–28], *Listeria* [29], malaria [30], as well as in models of malignancy [14,23,31,32]. Given these protective

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attributes, targeting T_{RM} to enhance vaccine responses represents a powerful approach to combatting infections and cancer.

Transcriptional regulation of CD8$^+$ T cell memory differentiation

Differential expression of CD127 and KLRG1 can be used to distinguish splenic effector CD8$^+$ T cell populations with differing memory potential [33,34]. KLRG1^{hi}CD127^{lo} cells comprise a shorter-lived, terminally-differentiated population of cells referred to as "terminal-effector" cells (TE), whereas KLRG1^{lo}CD127^{hi} cells are long-lived with the capacity for proliferation and self renewal, referred to as "memory-precursor" cells (MP) [35]. While circulating memory cells are primarily derived from the latter population, TE can persist for extended periods of time into the memory phase of infection [36]. A number of signals ranging from antigen exposure to inflammatory signals impact this bifurcation in CD8$^+$ T cell differentiation [35]. Further, it is apparent that multiple transcription factors (TFs) operate in concert to instruct MP vs. TE differentiation and circulating memory CD8$^+$ T cell fates. MP cells and T_{CM} are dependent on key TFs such as Id3 [37,38], TCF1 [39], Eomes [40,41], and Bcl6 [42] whereas optimal TE and T_{EM} differentiation requires Id2 [38,43], Blimp1 [44,45], T-bet [33], and Zeb2 [46,47] (Figure 1). As T_{RM} have emerged as a distinct memory subset, understanding how these canonical effector/memory TF relationships apply to T_{RM} has been somewhat unpredictable.

T_{RM} differentiation requires a "hybrid" of effector and memory cell transcriptional programs

The observation that early effector populations located in NLTs are predominantly KLRG1^{lo} led to the finding that T_{RM} are preferentially derived from KLRG1^{lo} cells [29,48,49]. Thus, one might expect shared TF programs between T_{RM} precursors and MP cells. However, it was recently demonstrated that early differentiating T_{RM} cells are transcriptionally distinct from MP cells [49]. Instead, and perhaps unexpectedly, it appears that T_{RM} utilize a hybrid TF differentiation program, requiring TFs associated with both memory and effector cell specification (Figure 1) [35,49–51]. For example, T-bet promotes TE/T_{EM} formation [33] but suppresses T_{RM} differentiation [19,26], whereas Blimp1 also promotes TE/T_{EM} formation [44,45] but is required for T_{RM} [52]. Conversely, pro-memory Eomes suppresses T_{RM} formation [19,35], but Nr4a1 which supports formation of MP/T_{CM} cells [53] is required for T_{RM} [54]. Further, other characteristics of T_{RM} seem to fit with this hybrid model. T_{RM} appear to be activated or effector-like by expressing elevated levels of CD69, PD-1, CTLA4, IFNγ, and GzB [49,55], reminiscent of early effector CD8$^+$ T cells or T_{EM}; yet, T_{RM} share some of the "stem-like" properties of T_{CM} in that they are long-lived and not terminally differentiated, giving rise to both T_{RM} and circulating memory cells upon transfer and reinfection into naive recipient mice [55]. Despite these overlapping features, T_{RM} are transcriptionally distinct from TE/T_{EM} and MP/T_{CM} [48,49]. Taken together, T_{RM} appear to "rewire" MP/T_{CM} and TE/T_{EM} TF-driven differentiation programs in order to sustain elevated effector function and long-term survival in NLTs.

It has become evident that TFs regulate multiple aspects of the T_{RM} differentiation pathway, which broadly consists of: 1) NLT trafficking, 2) *in situ* differentiation and retention, and 3)

long-term maintenance within NLTs (Figure 2) [56,57]. Understanding the molecular processes underlying T_{RM} differentiation and maintenance are critical for promoting T_{RM} in a therapeutic setting, and may reveal insights into the seemingly hybrid nature of T_{RM}.

Trafficking to NLTs

Within draining lymph nodes (dLNs), naive pathogen-specific $CD8^+$ T cells recognize cognate antigen in the context of MHC class I on antigen-presenting cells, which triggers subsequent $CD8^+$ T cell activation and clonal expansion. Transient suppression of the TF KLF2 results in downregulation of the KLF2-target gene, *S1pr1* [58,59]. S1PR1 promotes dLN egress through sphingosine 1 phosphate (S1P) chemotactic gradients, and thus suppressed S1PR1 expression results in prolonged retention in the dLN, allowing for optimal priming of antigen-specific $CD8^+$ T cells [60]. Upon receiving sufficient activation signals, clonally expanded $CD8^+$ T cells are either programmed to traffic to infected sites or express LN homing molecules, such as CD62L and CCR7, to support continued surveillance of secondary lymphoid organs [61,62].

Within dLNs, $CD8^+$ T cell expression of tissue-homing factors facilitates migration to distinct NLTs, which can be regulated by the initial dendritic cell priming [63]. For example, upregulation of CCR9 in the mesenteric LN (gut dLN) [64] sensitizes cells to CCL25 chemotactic gradients secreted in the intestinal epithelium, and $\alpha4\beta7$ integrin expression on $CD8^+$ T cells allows binding to the mucosal adressin cell-adhesion molecule (MAdCAM) on intestinal post-capillary venules [62,65]. Alternatively, in skin dLN, chemokine receptors such as CXCR6 and CCR10 [66,67] as well as a variant of the P-selectin ligand, CLA, are associated with $CD8^+$ T cell epidermal homing [62,68]. In peripheral blood, expression of integrin molecules and other cell-cell adhesion molecules facilitate extravasation into infected tissues [6] wherein T_{RM} differentiation ensues.

Retention and differentiation

Upon NLT localization, T cells must adapt to unique microenvironmental cues including diverse cytokine and nutrient milieus as well as low oxygen tension [22,35,69]. Indeed, by day 7 of LCMV infection, effector cells located in non-lymphoid sites are distinct from peripheral blood or splenic-localized effector cells both at the levels of gene-expression and chromatin accessibility [49]. Therefore, entry into NLTs triggers rapid changes in gene-expression programs linked to tissue-residency and adaptation to NLT microenvironments.

Although lymphoid-derived $KLRG1^{lo}$ cells preferentially give rise to T_{RM} [48,49], it is currently unclear which NLT-localized effector cells develop into mature long-lived T_{RM}, exit NLT, or undergo apoptosis. Nevertheless, $CD8^+$ T cells must engage tissue-retention programs and suppress tissue-egress in order to be maintained in NLTs [59]. Parabiosis studies, wherein the vasculature of two mice are conjoined, have demonstrated that $CD8^+$ T_{RM} populations do not equilibrate between NLTs [3,59]. Further, memory $CD8^+$ T cells contained within skin, dorsal root ganglia, or small intestine grafts do not equilibrate with host tissues upon transplant [20,70,71]. Therefore, once $CD8^+$ T cells become lodged in NLTs they do not recirculate, and this is the essence of what defines $CD8^+$ T cells as T_{RM}.

Prototypical T_{RM} retention factors include the integrin molecule CD103 (encoded by *Itgae*) and the glycoprotein CD69. CD103 expression, induced by TGFβ [48,72,73], is thought to mediate tissue retention through binding to E-cadherin molecules expressed on epithelial cells [74,75], whereas CD69 antagonizes S1PR1-mediated tissue egress [76,77]; while CD103- or CD69-deficiency can impact T_{RM} formation [48,73], they are not essential for all T_{RM} populations [3,69]. Early upregulation of CD103 may signify a T_{RM} -precursor population as these cells are $KLRG1^{lo}$, $Bcl2^{hi}$, and likely have an advantage of enhanced retention/survival [29,48,78]. Conversely, retention also requires downregulation of the KLF2 egress program, including suppressed expression of S1PR1, CCR7, and CD62L [48,59]. Utilizing a KLF2-reporter system, Skon *et al.* demonstrated that expression of KLF2 is rapidly suppressed upon NLT infiltration, and forced expression of S1PR1 impairs formation of T_{RM} in a variety of NLTs during LCMV infection [59]. Repression of the KLF2-S1PR1 egress program appears to be a common target among multiple TFs supporting T_{RM} differentiation. This is highlighted by the finding that Blimp1 and its homolog Hobit have recently been shown to synergistically regulate T_{RM} differentiation by controlling tissue egress [52]. Mackay *et al.* demonstrated that dual deletion of Blimp1 and Hobit impaired T_{RM} maintenance in the skin through suppression of genes such as *Klf2*, *S1pr1*, and *Ccr7*. Disruption of Blimp1 and Hobit expression impairs $CD8^+$ T_{RM} formation in multiple NLTs as well as liver NKT cell residency, providing evidence of a shared tissue-residency program among different tissues and cell types [52].

In line with findings that Blimp1/Hobit universally regulate lymphocyte residency, we have recently demonstrated that Runx3 is also required for T_{RM} differentiation in a range of NLTs [49]. Through computational and RNAi screening approaches, Runx3 was identified as a putative regulator of T_{RM} and functionally validated through inducible deletion approaches. Runx3 was critical for promoting expression of key tissue-residency factors such as CD103, CD69, and Blimp1 while suppressing T-bet expression as well as tissue egress molecules including KLF2, S1PR1, and CCR7. Of interest, it has been demonstrated that differentiation of intestinal ILC1 and ILC3 subsets as well as liver NK cells requires Runx3 [79,80], and Runx3 is critical for intestinal localization of $CD4^+$ T cells [81,82]. Further, Runx3 regulates the formation of skin-localized γδ T cells [83]. Taken together, Runx3 also appears to be a central regulator of tissue-residency in diverse immune cell types across multiple NLTs.

Interestingly, T-box transcription factors, T-bet and Eomes, have been shown to suppress T_{RM} formation [19]. Suppression of T-bet and Eomes is critical for optimal TGFβ signaling in differentiating skin T_{RM}, and forced expression of T-bet or Eomes impairs skin T_{RM} formation. Further, it was demonstrated that homozygous or heterozygous deletion of *Tbx21* (encoding T-bet) enhanced T cell lodging in the skin [19]. Laidlaw *et al.* demonstrated that T-bet-deficiency also enhances T_{RM} differentiation in the lung following influenza infection, and forced T-bet expression impaired formation of T_{RM} [26]. The role of T-bet in T_{RM} differentiation is likely multifaceted as it also may directly suppress *Itgae* (encoding CD103) expression [26].

A number of other TFs are important in the differentiation of T_{RM}. It was demonstrated that loss of AHR in $CD8^+$ T cells impairs the formation of skin T_{RM} [84], and it is likely AHR is

important for T_{RM} in multiple NLTs as it is also upregulated in intestinal T_{RM} cells [49,52]. The orphan nuclear receptor TFs Nr4a1, Nr4a2, and Nr4a3 are among the most differentially expressed TFs in intestinal T_{RM} relative to splenic T_{CM}, and are highly upregulated in T_{RM} from other sites [48,49]. In connection, loss of Nr4a1 resulted in impaired T_{RM} formation in the intestine and liver [30]. Further, Nr4a2 and Nr4a3 were also indicated to have important roles in supporting T_{RM} differentiation as RNAi impaired $CD8^+$ T cell accumulation in the intestine relative to splenic memory cells in a loss-of-function screening approach [49]. Further, Egr2 [50] and Notch [85] TFs were required for optimal lung T_{RM} formation following influenza infection. Transcriptional profiling of T_{RM} populations has also yielded insight into additional putative regulators of T_{RM}. Consistent with a hybrid TF program, Zeb2 (pro-TE) and TCF1 (pro-MP) are expressed at lower levels in T_{RM} relative to circulating cells, whereas IRF4 (pro-TE) and Bcl6 (pro-MP) are upregulated in T_{RM} [49]. As novel roles for TFs regulating T_{RM} differentiation are uncovered and their functions elucidated, it will become clear if T_{RM} have rewired their transcriptional profile to support effector and memory TF programs simultaneously, or if their dual nature is indicative of distinct T_{RM} subsets overlooked by bulk transcriptional analyses.

Long-term maintenance

Following pathogen clearance, $CD8^+$ effector cells localized to NLT must maintain expression of retention programs and suppress egress. Although it is unclear at what point T_{RM} precursors become mature T_{RM}, it was shown through principal component analysis of gene expression that the transcriptional signature of long-lived skin T_{RM} was predominantly established by day 25 of vaccinia infection [22]. The homeostatic demands of T_{RM} are also relatively unclear, though access to certain cytokines and changes in cellular metabolism may accompany long-term survival. T_{RM} have been shown to require canonical homeostatic cytokines IL-15 and IL-7 for survival [19,48,86], although IL-15 is not essential for T_{RM} in lymphoid tissues [87]. Despite the suppressive role of T-bet during NLT lodging, some level of expression is necessary for long-term T_{RM} survival through promoting CD122 expression and IL-15 responsiveness [19]. Further, TGFβ-signaling is critical for T_{RM} differentiation in the intestine, skin, and kidney, and thus continual access to TGFβ beyond early T_{RM} differentiation is presumably required for long-term maintenance [19,72,73,88]. Given the importance of TGFβ, IL-7, and IL-15 signaling in promoting and maintaining T_{RM}, it is likely certain downstream SMAD- and STAT-family TFs are required for T_{RM} formation and maintenance; however, SMAD4 was shown to be dispensable for T_{RM} [89].

The microenvironment of NLTs is distinct from that of lymphoid tissues or blood, including differences in nutrient availability and oxygen tension [90]. It was recently demonstrated that mature T_{RM} acquire exogenous free fatty acids through expression of FABP4 and FABP5, which are subsequently oxidized to fuel energetic demands required for T_{RM} survival in the lung and skin [22]. Further, mTOR activity is essential for optimal T_{RM} generation as rapamycin treatment blunts their formation [91]. However, it is unclear what other metabolic adaptations are required for T_{RM} survival in diverse NLT microenvironments or which TF programs sustain altered expression and activity of key metabolic enzymes.

One difficulty with identifying regulators of T_{RM} maintenance is that many genes required for long-term T_{RM} homeostasis are also linked to NLT retention and early differentiation. Therefore, disruption of key TFs often impairs differentiation, which impedes the assignment of functional roles in maintenance and longevity. Utilizing a tamoxifen-inducible deletion system, it was recently demonstrated that Runx3 is also important for T_{RM} maintenance in addition to controlling early differentiation [49]. Hobit and AHR also appear to be critical for later maintenance phases of T_{RM} development [52,84]. A deeper understanding of T_{RM} heterogeneity may provide insight into the dynamic requirements for certain TFs, helping to answer questions such as: 1) Do T_{RM} continuously mature over time, changing the kinetic requirements of certain TF? or 2) Are there long-lived and short-lived subsets of T_{RM} that have distinct TF requirements?

Targeting transcriptional programming of T_{RM} to combat disease

Given the sentinel role of T_{RM} in host protection, developing approaches to induce T_{RM} is an attractive avenue for enhancing vaccine efficacy [62]. Further, it has become evident that promoting or repressing tissue-residency of $CD8^+$ T cells may be relevant in non-infectious settings ranging from cancer to inflammatory diseases and autoimmunity [62]. The tumor microenvironment holds parallels to NLTs (relative to lymphoid organs) including lower oxygen tension, nutrient availability, and a distinct cytokine milieu (e.g. TGFβ) [90,92]. In connection, it has been demonstrated that tumor infiltrating lymphocytes (TILs) share certain features of T_{RM} [93,94], and that a T_{RM}-like gene expression program in TILs is linked to better prognoses in lung cancer patients [95]. T_{RM} express elevated levels of effector molecules such as GzB, IFNγ, and FasL relative to circulating cells [49,55], which is another characteristic of T_{RM} that would benefit the anti-tumor function of TILs [95]. In connection, we have demonstrated that Runx3 is critical for $CD8^+$ T cell accumulation in tumors and is key in programming expression of genes that support tissue-residency and cytotoxic function of TILs [49]. Therefore, targeting TFs that orchestrate multiple aspects of the T_{RM} program could enhance the efficacy of adoptive cell therapies against malignancies.

In other instances, the potent inflammatory and cytotoxic capacity of $CD8^+$ T cells in NLTs can be harmful [62]. In autoimmune or inflammatory diseases such as diabetes, psoriasis, or inflammatory bowel disease, $CD8^+$ T cells residing in the pancreas [96], skin [22,61], or intestine [92] likely acquire aspects of tissue-residency reprogramming, albeit they likely are not true memory cells (as the term T_{RM} implies) given the presence of persistent self-antigen. Indeed, conditions that impair T_{RM} formation such as CD103-deficiency [97] or rapamycin treatment [91] have also been shown to alleviate pathology in models of intestinal inflammation/autoimmunity. Further, T_{RM} have been shown to mediate rapid contact hypersensitivity in the skin [61]. Notably, other related conditions include metabolic diseases in which $CD8^+$ T cells localize to inflamed white adipose tissue [98] or atherosclerotic lesions [99] and further potentiate inflammation. Taken together, manipulating T_{RM} TF programs to block engagement of tissue-residency features could be beneficial in these contexts.

Conclusions

T_{RM} have emerged as key mediators of long-lived immunity. Given the expansive role of TFs in regulating expression of diverse molecules critical to $CD8^+$ T cell residency in NLTs, defining novel functions for TFs in controlling T_{RM} differentiation will likely enhance our ability to treat complex T cell mediated-diseases and yield important information regarding the ontogeny, function, and hybrid nature of T_{RM}. Further, parsing out overlapping requirements of $CD8^+$ T cell tissue-residency in healthy (following acute infection) and diseased (e.g. tumors or autoimmunity) non-lymphoid settings may be conceptually useful in studying T_{RM} development and informing approaches to improve adoptive cell therapies or suppress inflammatory/auto-reactive $CD8^+$ T cell populations.

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Highlights

- The T_{RM} transcriptional differentiation program employs drivers of both effector and memory T cell subsets
- Early differentiating T_{RM} are transcriptionally distinct from circulating memory-precursor cells
- Blimp1, Hobit, and Runx3 are central regulators of tissue-residency across multiple immune cell types and non-lymphoid sites
- Promoting or suppressing $CD8^+$ T cell residency in non-lymphoid tissues may be a therapeutic strategy to treat cancers or prevent inflammatory diseases

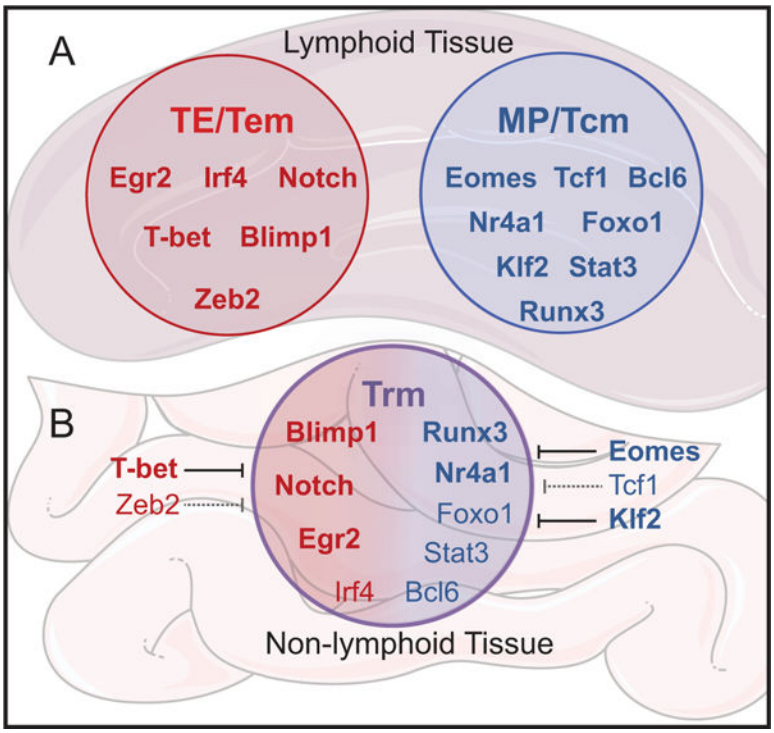

Figure 1. T_{RM} exhibit a hybrid effector/memory TF-driven differentiation program

A, Key TFs with known functions in controlling TE vs. MP differentiation are highlighted. **B**, TFs critical to T_{RM} differentiation are included (inside the circle) or that suppress T_{RM} development relative to circulating memory (outside the circle). Additionally, TFs that are predicted to be required for T_{RM} differentiation based on gene expression [49] (inside the circle) or predicted to suppress T_{RM} differentiation (outside the circle) are included. TFs with validated roles are bolded whereas predicted regulators are not.

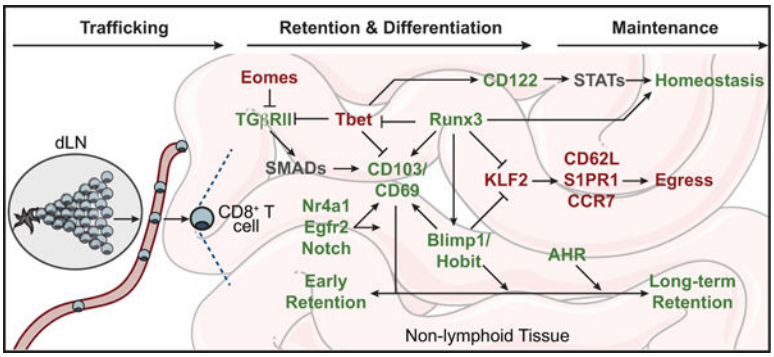

Figure 2. TF regulation of T_{RM} differentiation

TFs with established roles in promoting T_{RM} are highlighted in green, those repressing T_{RM} are highlighted in red, and putative regulators are gray. dLN; draining lymph node.