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Remembering to remember: T cell memory maintenance and plasticity

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Abstract

Upon activation, naive T cells give rise to a heterogeneous cell population of effector and memory T cells that mediate antigen clearance and provide long-lived protection from rechallenge. Many of the transcriptional regulators that direct the differentiation of naive T cells to acquire the range of phenotypic and functional characteristics of effector and memory T cells have been described. However, the active programs that maintain the specific subsets of memory T cells are less clear. Here, we discuss recent studies that suggest effector and memory $CD8^+$ T cells exist in cellular 'states' with inherent plasticity. Further, we consider the newly identified role of active transcriptional and epigenetic programming in maintaining the identity of the distinct subsets within the memory population.

Introduction

Essential for the elimination of intracellular pathogens and malignant cells, $CD8^+$ T cells are an important component of the adaptive immune response. Upon activation, antigen-specific $CD8^+$ T cells proliferate and differentiate into a heterogenous population of effector cells that provide protection through cytolytic activity and the secretion of inflammatory cytokines [1]. A portion of the effector cell population has been considered to be terminally-differentiated—providing immediate, acute function, then undergoing apoptosis at the resolution of the infection or shortly thereafter. In contrast, other cells are programmed for long-term survival after the contraction of the effector population to afford durable immunological protection [1]. Heterogeneity in phenotype, function, location, and trafficking ability is also observed within the long-lived memory population [2]. Subsets within the effector or memory $CD8^+$ T cell populations have largely been considered to be cellular 'fates' with fixed differentiation paths. However, recent studies suggest that $CD8^+$ T effector and memory populations consist of cells in 'states' that require reinforcement by active regulatory programs which, when lost, reveal significant 'plasticity' among the distinct subsets. Understanding the functional heterogeneity that exists within the effector

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and memory T cell population and their corresponding differentiation paths and maintenance programs will allow for efficient design of T cell-based vaccines and adoptive therapies targeting emerging infectious diseases and cancers.

$CD8^+$ T cell heterogeneity

The population of cells with effector function at the peak of infection exhibits substantial phenotypic and functional diversity [3,4], and considerable effort has been made to define cellular phenotypes that predict the 'fate' of an effector T cell following resolution of the infection. Expression of KLRG1 and CD127 can be used to delineate the memory potential of effector $CD8^+$ T cells [5–8]. In transfer experiments, $CD8^+$ T cells with high expression of CD127 and low expression of KLRG1 ($KLRG1^{lo}CD127^{hi}$) were found to have a significantly greater capacity to survive following infection compared to the $KLRG1^{hi}CD127^{lo}$ counterparts and exhibited stem-like properties such as multipotency and the capacity for proliferation and self-renewal [5,9,10]. Although both express cytokines and cytolytic molecules, $KLRG1^{lo}CD127^{hi}$ $CD8^+$ T cells define a pool of memory precursors (MP) while the $KLRG1^{hi}CD127^{lo}$ subset represents terminal effector (TE) cells that are more likely to die following the resolution of infection. This demarcation is by no means precise as further heterogeneity exists within the TE and MP cell populations [6], and TE cells do persist following infection at memory time points [11–13]. Furthermore, KLRG1 and CD127 are not necessary or sufficient to drive generation of the TE or MP $CD8^+$ T cell populations, respectively [8,14]. Early expression of additional molecules has also been employed to predict the differentiation path of effector $CD8^+$ T cells. Expression of the transcriptional regulator Id3 or TCF1 and reduced levels of IL-2Rα bias an effector $CD8^+$ T cell to a longer-lived memory T cell state [15–18].

The memory population that persists after pathogen clearance is also comprised of cells with a range of phenotypes. Several approaches have been applied to categorize these cells based on phenotype and function, and at least 5 subsets have been identified (Table 1). Traditionally, the circulating $CD8^+$ memory T cells have been divided into two broad subsets, effector memory (T_{EM}) and central memory (T_{CM}), based on anatomical location, expression of cell-surface molecules and effector function [19]. T_{EM} lacking CD62L and CCR7 were originally described to continually recirculate through non-lymphoid tissues and blood surveying for reinfection. With the ability to elicit direct effector function, T_{EM} would be poised to provide immediate protection should reinfection occur [19,20]. $CD62L^{hi}CCR7^{hi}$ T_{CM} are a long-lived subset that can traffic to secondary lymph nodes, have the ability to self-renew, and exhibit a high proliferation capacity upon reactivation [19,21–24]. Recently, surface expression of the chemokine receptor, CX3CR1, was used to refine this classification [25,26]. While classically defined T_{EM} and T_{CM} exhibit high or no CX3CR1 expression, respectively, a novel $CX3CR1^{int}$ subset was recently identified and termed peripheral memory T cells (T_{PM}) [26]. T_{PM} show a superior steady-state self-renewal capacity and can proliferate in a recall response to comparable levels as the $CX3CR1^-$ T_{CM} population [26], but have functional abilities such as IL-2 secretion and cytotoxicity intermediary between T_{CM} and T_{EM}. Interestingly, T_{PM} were found to preferentially surveil the non-lymphoid tissues presumably using a unique pattern of migration from blood to tissue to lymph [26]. Within this scheme, the $CX3CR1^{hi}$ T_{EM} population appeared primarily

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restricted to the intravascular space [25,26] and presumably the spleen. These data emphasize that the T_{EM} population as defined in much of the literature likely contains subsets of cells with distinct trafficking patterns and functional characteristics and highlight the pitfalls associated with phenotypic-based classifications in this context. An additional non-circulating, resident-memory (T_{RM}) subset has also been described that is likely the prominent memory T cell type residing in the non-lymphoid tissues without recirculating, providing the first-line of defense upon pathogen reinfection (reviewed in [27]). Finally, a memory T stem cell (T_{SCM}) population has been described in both human and mouse [28–31]. In some contexts, T_{SCM} are concealed within the $CD44^{lo}CD62L^{hi}$ naive T cells pool but can be identified by their expression of stem cell antigen-1 (Sca-1), B-cell lymphoma protein-2 (Bcl-2), and CD122. Like stem cells, T_{SCM} are multipotent able to generate TE, T_{EM} and T_{CM} subsets, and have the ability to self-renew [29].

As noted above, T cells with the phenotype of TE T cells are often present for extended periods of time following infection (Long-lived effector cells) and contribute to $CD8^+$ T cell recall responses. Specifically, a $CD27^{lo}CD43^{lo}$ T cell population with effector-like attributes, including high expression of KLRG1, T-bet, and granzyme B, but lo/intermediate levels of CD127, has been described [11,32]. Following a primary response, these cells eventually decline; however, boosting greatly enriches the frequency of this population. Despite weak proliferative ability, these cells provide cytolytic-dependent control of certain acute pathogens including *Listeria monocytogenes* and vaccinia virus [11]. CX3CR1 expression inversely correlates with the degree of effector T cell differentiation [25,26] so the long-lived effector cells likely are included in the $CX3CR1^{hi}$ classification of memory T cell subsets.

While the use of the defined populations introduced here proves useful in the discussion of the molecules involved in establishing and sustaining $CD8^+$ memory T cell responses, it is increasingly apparent that subset heterogeneity is vast and can be flawed as functional and trafficking attributes often span phenotypic subgroups [33]. Thus, it is expected that our understanding of effector and memory T cell differentiation will continue to evolve reflecting perhaps instead a continuum of effector functions, recirculation patterns, and longevity/selfrenewal characteristics.

Transcriptional regulation of effector and memory $CD8^+$ T cells

T cells responding to infection will integrate multiple diverse signals including those from antigen exposure, costimulation and the cytokine and tissue microenvironmental milieu that ultimately influence the final states of the progeny, directing the heterogeneity within the effector and memory T cell populations. Importantly, transcriptional programs are induced that instruct the commitment of a T cell to a particular effector or memory T cell subset (reviewed in [1,34]). Numerous transcription factors have been defined that instruct $CD8^+$ T cell differentiation—formation of MP and T_{CM} subsets require key transcriptional regulators such as Id3 [15,35], TCF1 [17,18], Eomesodermin [36,37], FOXO1 [38] and Bcl6 [39] whereas TE and T_{EM} cell differentiation is supported by Id2 [40–42], Blimp1[43,44], T-bet [6] and Zeb2 [45,46]. However, the transcriptional regulation that is necessary to maintain

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the phenotypic and functional characteristics of the cellular subsets once established has not been studied as extensively.

Memory CD8+ T cell maintenance

Homeostasis of the persisting memory T cells is a key component of their ability to provide durable protection from reinfection. Memory T cells are maintained in an antigen-independent manner; however, their homeostasis is supported by the cytokines IL-7 and IL-15 [47]. IL-7 and IL-15 initiate the downstream JAK-STAT signaling cascade and subsequently activate transcription factors that promote homeostatic proliferation and survival of T cells by regulating expression of proliferation-associated, anti-apoptotic and pro-apoptoic genes [47]. Further, IL-7 has been shown to support the metabolic fitness of memory T cells. IL-7 induces expression of the glycerol channel aquaporin 9 in antigen-specific memory T cells allowing for uptake of glycerol for use in triglyceride synthesis and storage to meet the metabolic requirements of memory T cells [48]. Interestingly, human and mouse T_{RM} have recently been shown to uniquely express high levels of fatty-acid binding proteins 4 and 5 (FABP4/5) that mediate lipid uptake and intracellular transport [49]. Skin T_{RM} but not T_{CM} deficient for both FABP4/5 were unable to take up exogenous free fatty acid and failed to persist suggesting that oxidative metabolism of exogenous FFAs is required for T_{RM} to survive long-term in the peripheral tissues [49]. The purinergic receptor, P2RX7, has also recently been shown to be important for directing mitochondrial homeostasis and metabolic function in differentiating T_{CM} and T_{RM} populations in mice [50]. Importantly, mice transiently treated with a pharmacological inhibitor of P2RX7, a promising therapy to treat neuropathic pain, from day 40 to 50 following LCMV infection resulted in a loss of the established T_{CM} population suggesting a necessary role in memory maintenance [50].

What additional transcription factors and downstream cellular processes these affect in memory T cells to assure longevity and robust recall responses remain to be fully appreciated. Importantly, the regulatory programs necessary to maintain the substantial diversity that exists within the effector and memory $CD8^+$ T cell populations are only beginning to be defined. While precursors within the effector T cell population predetermined to give rise to the distinct memory subsets can be identified, plasticity between $CD8^+$ T cell fates also has been demonstrated. Recent technological advances have allowed for the initiation of a more thorough examination of these important aspects of $CD8^+$ T cell memory. Here we describe several studies that have utilized novel fate-mapping strategies and epigenetic profiling techniques to examine origin and subsetspecific long-term maintenance of $CD8^+$ T cell memory.

Fate-mapping

Memory populations may be derived from a discrete group of memory precursors that arise from naive T cells following infection as early as the first division following T cell activation [51]. T_{CM} and T_{EM} have been suggested to chiefly differentiate from the $KLRG1^{lo}CD127^{hi}$ MP T cells and T_{RM} from a $KLRG1^{lo}$ precursor [52–54]. In support of T cells having a predefined precursor-product relationship, Smith *et al.* showed that a T cell's fate may be

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imprinted during development and be contingent at least in part on which time in life the precursor undergoes thymic maturation [55]. For this study, a new fate-mapping mouse model was established whereby a CD4 promoter-driven inducible cre recombinase could direct expression of red fluorescent protein TdTomato (RFP) in $CD4^+CD8^+$ double positive thymocytes upon tamoxifen treatment. In this way, a wave of newly developing $CD8^+$ T cells were 'timestamped' and could be followed in the periphery [55]. Importantly, the authors found that T cells made during infancy exhibited more rapid effector-like qualities while T cells generated during adulthood more efficiently seeded the long-lived memory pool. The fate choice defined by the T cell's developmental origin was governed by a unique transcriptional profile and chromatin landscape [55].

Fate commitment and terminal-differentiation of T cells has been questioned and the notion that naive T cells give rise to an effector population where at least a portion of T cells maintain the flexibility to 'dedifferentiate' following resolution of the infection to seed the memory pool should be considered. Maintaining some degree of developmental plasticity would potentially drive functional heterogeneity within the memory T cell population. In support of this, a portion of TE cells can re-express CD127, suggesting that epigenetic remodeling and a loss of repressive marks from pro-memory genes can occur [6,12,13] . As well, memory lineage interconversion has been observed where $CD62L^{lo}$ T_{EM} cells, considered to be more differentiated, converted to a $CD62L^{hi}CCR7^{hi}CD27^{hi}$ T_{CM} phenotype in a proliferation-independent manner in the absence of antigen [21]. However, this observation was recently revised when memory T cells were subsetted based on CX3CR1 [25,26]. T_{EM} with high expression of CX3CR1 were unable to adopt a $CD62L^{hi}$ T_{CM} phenotype when transferred to a new host. Yet, some $CX3CR1^{int}$ or $CX3CR1^-$ T cells could upregulate CD62L and join the T_{CM} pool [26]. These findings support the idea that the phenotypic states among memory populations may not be fully stable and may be subject to additional regulation after the acute phase of infection.

In line with these findings that effector T cells do not necessarily have a fixed fate, we [12] and others [13] have examined the stability of 'terminally-differentiated' $KLRG1^{hi}$ effector $CD8^+$ T cells and demonstrated plasticity within TE or long-lived effector T cells with the ability to convert into memory T cell populations in specific contexts. Using a KLRG1-cre reporter system that allows longitudinal tracking of $KLRG1^{hi}$ effector T cells throughout infection and memory development, T cells that lost KLRG1 expression during the late effector and contraction phase of infection—termed exKLRG1 T cells—were seen to make up 20–40% of the memory T cell population following Listeria monocytogenes or Vesicular stomatitis virus infection and persisted longer than the $KLRG^{hi}$ T cells that were observed at memory time points [13]. ExKLRG1 T cells preferentially differentiated from effector T cells that also expressed CD127, and reminiscent of $KLRG1^{hi}CD127^{hi}$ double positive effector cells, expressed intermediate levels of Gzmb, T-bet, KI67, Bcl-2, Zeb2, Blimp1, and Bach2. ATAC-seq analysis revealed that exKLRG1 had open chromatin regions at both effector and memory-related gene loci. This seemingly allows the $exKLRG1^{hi}$ to efficiently generate most memory populations including T_{CM}, T_{EM}, T_{PM} and T_{RM} while preserving their effector-like past, permitting early participation in a secondary response [13]. Bach2, a transcriptional repressor shown to restrain terminal differentiation and promote memory formation in lymphocytes [56–58] appears to promote this developmental plasticity in $CD8^+$

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T cells and plays a role in the development of exKLRG1 memory cells from $KLRG1^{hi}CD127^{hi}$ effector T cells in an AKT-mTOR-FOXO1 dependent manner [13].

We have further demonstrated the necessity for continued transcriptional regulation to sustain the differentiated state of a $CD8^{+}$ T cell following acute viral infection [12]. The inhibitor of E protein transcription factors Id2, is expressed by effector $CD8^{+}$ T cells to promote survival and terminal differentiation [40–42]. Notably, Id2 is also expressed by $CD8^{+}$ T cells into the memory phase following infection to maintain the 'effector-like' $KLRG1^{hi}$ $CD8^{+}$ T cell population. We used a tamoxifen-inducible knock-out mouse model in order to control the timing of Id2 deletion. Induced deletion of Id2 following resolution of lymphocytic choriomeningitis virus infection transformed the $KLRG1^{hi}$ long-lived TE and T_{EM} subsets into a $KLRG1^{lo}$ population with the phenotype and gene expression program resembling that of the T_{CM} memory subset [12]. Thus, constant Id2 regulation of E protein activity supports the persistence of an 'effector-like' memory population while preserving some degree of cellular plasticity that allows these cells to 'dedifferentiate' and reacquire expression of genes characteristic of the long-lived memory populations if inhibition of E proteins by Id2 is lost [12].

Conversely, continual reinforcement of the memory state has also been suggested to be necessary [59,60]. Induced deletion of the transcription factor FOXO1 in memory $CD8^{+}$ T cells caused a reversion to a cell state reminiscent of terminally-differentiated effector T cells with increased KLRG1 and decreased CD62L expression in a proliferation independent manner. These cells also produced more granzyme B [59] and less IL-2 [60], and seemingly reverted away from the characteristic T_{CM} memory state. As well, FOXO1-deleted memory T cells gradually declined in number as continuous FOXO1 expression was necessary to support the expression of pro-survival molecules and enable homeostatic turnover. Further, they had a greatly reduced re-expansion capacity, presumably due to a defect in proliferation or trafficking to secondary lymphoid organs where re-expansion takes place [60]. We have also demonstrated that the transcription factor Runx3 is important for the maintenance of T_{RM} in nonlymphoid tissues [61]. Induced deletion of Runx3 in established small intestine T_{RM} led to a significant loss of $CD69^{+}CD103^{+}$ cells likely due to an increased rate of apoptosis [27].

Taken together, these studies indicate that memory T cell 'fates' may not be absolute but rather an active process with regulatory networks working to uphold the memory cell 'state'. This then raises the question of what signals are required to set up and sustain the reinforcement of memory cell states and can these be manipulated in the context of vaccination or immunopathology.

Epigenetic profiling

While several studies have worked to define the transcription programs necessary to uphold the subset-specific phenotypic and functional properties of memory $CD8^{+}$ T cells, others have focused on the epigenetic modifications of histones and DNA that regulate the chromatin accessibility for those subset-defining transcription factors. DNA methylation is one such alteration that fixes genes in an 'off' position thus silencing expression. Histone modifications can promote repressive or permissive chromatin states, depending on the

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combination. For example, trimethylation of lysine 4 (H3K4me3) marks active promoters and is associated with gene expression while trimethylation of lysine 27 (H3K27me3) is associated with gene repression.

Once activated, a naive T cell may undergo epigenetic programming that drives differentiation of effector cells and expression of genes that mediate pathogen clearance while genes associated with naive or resting cells are repressed. TE $CD8^+$ T cells were found to epigenetically silence genes responsible for longevity and plasticity in part by the Polycomb Repressive Complex 2 (PRC2,) which catalyzes *de novo* repressive H3K27 trimethylation marks. Conversely, MP cells appeared to maintain permissive and active chromatin states at both MP- and TE-signature genes in a mechanism involving FOXO1 [62]. In a parallel study that used single-cell RNA sequencing to assess $CD8^+$ T cells over the course of a viral infection, EZH2, a catalytic subunit of PRC2, was found to be highly expressed in TE cells after the first division following T cell activation [63]. TE cells were seen to gain repressive H3K27me3 marks compared to naive T cells and Ezh2 binding was observed at genes—many previously linked to memory—with reduced expression at day 4 relative to first division TE cells [63]. Furthermore, PRC2 deficiency affected the differentiating TE or ‘effector-like’ cells while minimally impacted the memory T cell maturation [62,63]. This argues that $CD8^+$ TE cells restrict their fate while the MP population maintains multipotency to differentiate into memory cells that can turn-on effector function upon reactivation [62].

Two recent studies examined DNA methylation status to address the origin of human and mouse memory T cells and suggest that effector T cells dedifferentiate to seed the memory pool [64,65]. Youngblood *et al.* considered the observation that memory $CD8^+$ T cells are hybrid in nature—able to elicit effector functions upon rechallenge but also have naive-associated properties such as pluripotency and secondary lymphoid homing ability [65]. The on-off-on pattern of expression for naive-associated genes during naive-to-effector-to-memory differentiation was analyzed through whole-genome bisulfite sequencing (WGBS) to reveal the DNA methylation status for $CD8^+$ T cell subsets over the course of an infection [65]. Effector T cell subsets responding to infection were found to have increased regions of *de novo* DNA methylation at naive-associated loci in part by the action of the methyltransferase Dnmt3a, and canonical effector genes became demethylated [65]. Interestingly, the MP effector subset re-expressed naive-associated genes as they formed memory T cells, and this was associated with the erasure of the *de novo* DNA methylation that was acquired during the naive to effector T cell transition. Effector genes such as *Gzmb* and *Prf1* remained unmethylated in memory T cells despite their reduced expression levels [65]. While previous work showed that Dmnt3a drives a *de novo* DNA methylation program specific to effector TE cells [66], this new work supports the idea that effector cells with memory potential dedifferentiate into memory T cells that are able to re-express naive-associated genes [65]. Similarly, Akondy *et al.* noted that the human memory population originated from effector T cells that had extensively proliferated during the initial two weeks following administration of the yellow fever vaccine [64]. Additionally, shared features of the effector and memory T cell epigenetic profiles were observed with notable similarities in chromatin accessibility and DNA methylation. While the transcriptional signature of memory T cells was more like naive than effector—with the exception of TCR, cytokine and

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toll-like receptor mediated signaling pathways—the memory T cells retained epigenetic memory of differentiation through an effector stage and appear to dedifferentiate from a subset of fate-permissive, activated CD8^{+} T cells [64].

Once established, memory CD8^{+} T cell populations are maintained through active transcriptional programs and presumably supported by epigenetic modifications. Abdelsamed *et al.* examined the acquired DNA methylation marks in human T_{SCM}, T_{CM} and T_{EM} cells and how these are preserved during antigen-independent homeostasis [67]. WGS was performed on naive and memory T cells isolated from healthy donor blood. A unique methylation status was identified for each different memory populations; for instance, the *CCR7* and *CD62L* regions where significantly methylated in the T_{EM} population but remained predominately unmethylated in the T_{CM} and T_{SCM} subsets [67]. As well, the *DMNT3A* and *TCF7* promoters became progressively enriched for methylation as the memory subset became more differentiated (ie. $T_{SCM}<T_{CM}<T_{EM}$). However, loci of effector molecules were demethylated in all memory T cell subsets [67]. Following IL-7- and IL-15-driven *in vitro* homeostatic proliferation or adoptive transfer into transplant patients, the memory T cells maintained the effector-loci demethylation status [67]. Interestingly, in these experimental settings, the T_{CM} and T_{SCM} subsets differentiated towards a T_{EM} phenotype and also increased methylation at the *CCR7* and *TCF7* loci [67]. This suggests that certain epigenetic marks can remain stable over time while others can be modified for adaptation to environmental changes.

Maintenance of other immune populations

The requirement for active reinforcement of cell ‘state’ by transcriptional networks is not unique to the CD8^{+} T cell population. In fact, heterogeneity and plasticity have been described among the CD4^{+} T cell lineages. It is suggested that CD4^{+} T cells undergo subset specification but retain the ability to dynamically regulate their cellular ‘state’ in response to changing conditions. Cytokine signaling mediating STAT transcription factors and subsequent activation or repression of subset-specific transcriptional programs is a major driver of plasticity [68]. As an example, regulatory T cells (Treg) can be induced by environmental cues to express T helper cell subset defining transcription factors presumably to support Treg homeostasis and better regulate immune responses [68]. Further, in several inflammatory settings, Treg can become unstable, lose Foxp3 expression and acquire an effector phenotype [69]. As well, induced deletion of Foxp3 in mature Tregs results in a loss of suppressive function and conversion to an effector T cell able to produce IL-2 and T helper type 1 cytokines [70]. Similarly, active regulation by transcription factors in innate lymphoid cells (ILCs) ensures subset-specific phenotypes and functional plasticity can occur as a result of cytokine stimuli likely to fine-tune the immune response [71]. While continual GATA-3 regulation [72,73] has been shown to support ILC homeostasis and T-bet, Rorγt, Notch transcription factors can mediate ILC subset conversion [71], additional transcriptional and epigenetic regulators reinforcing these ‘states’ have yet to be identified.

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Conclusion

Heterogeneity within lymphocyte populations is important for fighting a diverse array of infections (Figure 1). Maintaining developmental plasticity within memory T cell subpopulations allows for interpretation of environmental signals and affords the T cell compartment the capacity to evolve the most effective response. While recent work described above favors the re-examination of the notion that $CD8^{+}$ T cells irreversibly commit to a particular cell ‘fate’ in the effector phase, it will be important to clearly understand the transcriptional and epigenetic programs in place that dictate stability or pliability of a memory T cell. While this review focuses on memory homeostasis, additional complexity emerges when considering the secondary effector population. For instance, memory T cells removed from nonlymphoid tissue can give rise to circulating memory populations in a secondary response [74]. Further, in a secondary nonlymphoid tissue infection T_{RM} proliferate *in situ* producing secondary effector that maintain the T_{RM} population [75,76]. Additional studies will be necessary to understand the plasticity in secondary effector T cell subsets and the subsequent heterogeneity that may develop in the memory populations. Importantly, with this knowledge will come the ability to therapeutically reprogram T cell populations in the form of T cell-based vaccines and treatments against infectious and inflammatory diseases as well as malignancies.

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Highlights

- The effector and memory CD8^{+} T cell populations exhibit significant heterogeneity
- Effector and memory T cell subsets exist in 'states' and retain some degree of plasticity
- Active transcriptional regulation maintains the identity of the memory T cell subsets
- Epigenetic programming likely re-enforce memory T cell 'states'

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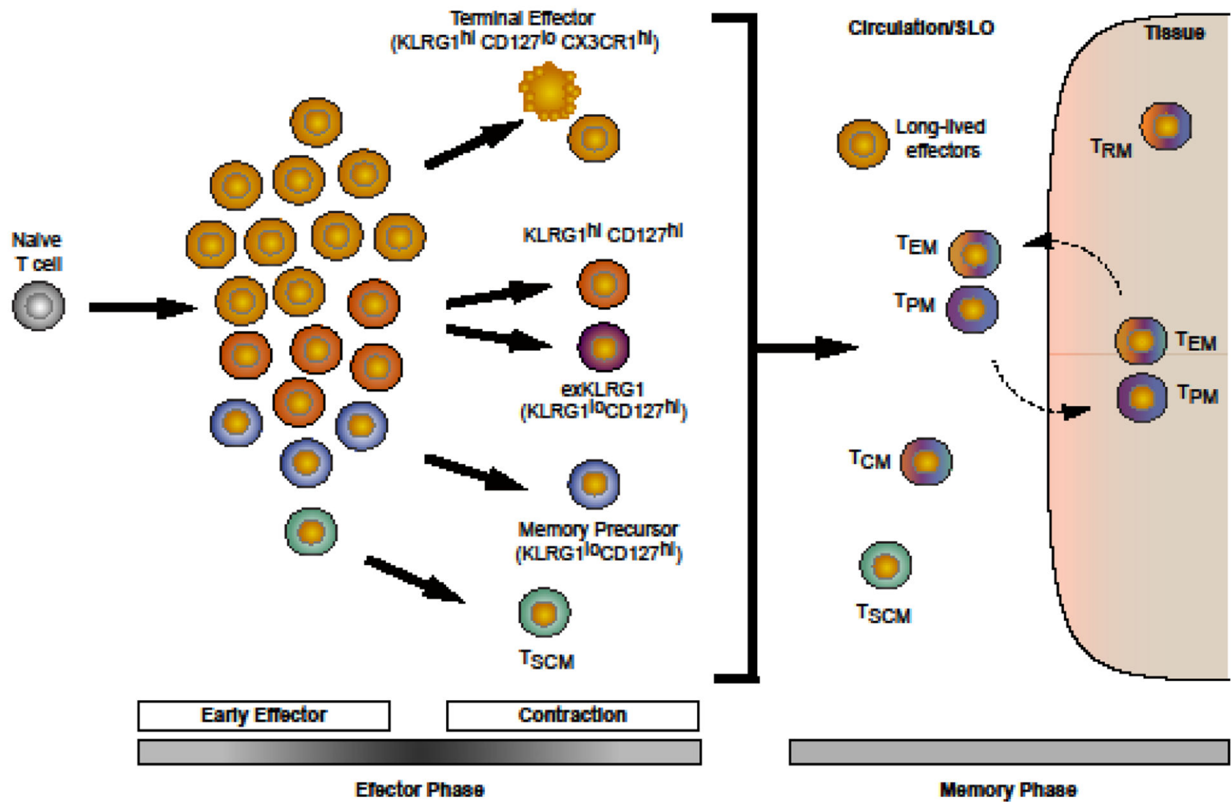

Figure 1. Heterogeneity within the effector and memory CD8+ T cell populations.

Activation of a naive T cell gives rise to phenotypically diverse effector T cells that contribute to the generation of the long-lived memory subsets. Memory T cells are represented with the corresponding effector precursor color that has a demonstrated role in that subset's formation. Memory T cells retain the epigenetic modifications acquired during the effector phase as indicated by yellow nuclei. T_{EM} = effector memory; T_{CM} = central memory; T_{PM} = peripheral memory; T_{RM} = resident memory; T_{SCM} = stem-cell memory.

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Table 1.

Memory T cell Subsets

Memory Subset	Phenotypic Markers	Properties
Long-lived Effectors [11,12,32]	$KLRG1^{hi}CD127^{lo/int}$ $CD27^{lo}CD43^{lo}$	High effector function Weak proliferative capacity
T_{EM} [19,25,26]	$CCR7^{lo}CD62L^{lo}$ $CX3CR1^{hi}CD127^{hi}$	Increased effector function Circulating - blood/spleen
T_{PM} [25,26]	$CD62L^{hi/lo}CX3CR1^{int}$ $CD127^{hi}$	High self-renewal capacity Increased proliferative capacity Intermediate effector function Circulating -tissues
T_{RM} [20]	$CD103^{hi/lo}CD69^{hi/lo}$ $CD127^{int}$	Proliferative capacity Increased effector function Resident - tissues
T_{CM} [19,25,26]	$CCR7^{hi}CD62L^{hi}$ $CX3CR1^{lo}CD127^{hi}$	Increased proliferative capacity Self-renewal ability Circulating - SLO
T_{SCM} [28,31]	$CD44^{lo}CD62L^{hi}Sca\text{-}1^{hi}$ $CD122^{hi}$, $Bcl\text{-}2^{hi}$	High self-renewal capacity Multipotent

Note: CD127 and CX3CR1 are not necessarily conventional phenotypic marker of memory subsets but their differential expression has highlighted the heterogeneity in memory subsets that previously been under appreciated.