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REVIEW

Impact of multiple hits with cognate antigen on memory CD8+ T-cell fate

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Antigen-driven activation of CD8+ T cells results in the development of a robust anti-pathogen response and ultimately leads to the establishment of long-lived memory T cells. During the primary response, CD8+ T cells interact multiple times with cognate antigen on distinct types of antigen-presenting cells. The timing, location and context of these antigen encounters significantly impact the differentiation programs initiated in the cells. Moderate re-activation in the periphery promotes the establishment of the tissue-resident memory T cells that serve as sentinels at the portal of pathogen entry. Under some circumstances, moderate re-activation of T cells in the periphery can result in the excessive expansion and accumulation of circulatory memory T cells, a process called memory inflation. In contrast, excessive re-activation stimuli generally impede conventional T-cell differentiation programs and can result in T-cell exhaustion. However, these conditions can also elicit a small population of exhausted T cells with a memory-like signature and self-renewal capability that are capable of responding to immunotherapy, and restoration of functional activity. Although it is clear that antigen re-encounter during the primary immune response has a significant impact on memory T-cell development, we still do not understand the molecular details that drive these fate decisions. Here, we review our understanding of how antigen encounters and re-activation events impact the array of memory CD8+ T-cell subsets subsequently generated. Identification of the molecular programs that drive memory T-cell generation will advance the development of new vaccine strategies that elicit high-quality CD8+ T-cell memory.

Keywords: cognate antigen presentation, memory differentiation, re-activation, T-cell function, T-cell memory

Introduction

Naive CD8+ T cells that encounter cognate antigen in the draining lymph nodes (LNs) initiate an activation program that results in their clonal expansion and differentiation into subsets of functional effector cells. Although the majority of effector cells die after clearance of antigen, a small proportion of cells survive and persist as memory cells.

During their initial priming in the draining LNs, antigen-reactive CD8+ T cells receive a number of distinct signals depending on the affinity of T-cell antigen-receptor (TCR) for the peptide–major histocompatibility complex (MHC) complex, and the array of co-stimulatory molecules and cytokines encountered (1). Proliferating daughter cells subsequently receive further, distinct stimulatory signals as a consequence of asymmetric cell division and intraclonal competition (2–5). The strength of these signals also varies depending on the time post-infection, antigen distribution and the rate of antigen clearance. These spatially and temporary distinct stimulatory signals ultimately dictate the differentiation program of CD8+ T cells. For instance, strong antigen and inflammatory cytokine signaling induces the development of terminally differentiated effector cells that express killer cell lectin-like receptor G1 (KLRG1), but not IL-7 receptor alpha (CD127). In contrast, cells that receive weaker signals preferentially differentiate into memory precursors (KLRG1− CD127+) (Table 1) (6, 7). The formation of these subsets is regulated, at least in part, by the reciprocal expression of transcription factors, such as T-bet and Eomes. Signaling mediated by the TCR and IL-12 induces the up-regulation of T-bet, but repression of Eomes, leading to terminal effector differentiation (6, 8), whereas sustained expression of Eomes, which is also amplified by IL-2, supports differentiation into memory (9–11). Other transcription factors, such as Blimp-1, Bcl-6, Id2, Id3, STAT3, STAT4 and FOXO1, are also involved in effector/memory differentiation and are reviewed elsewhere (2). Some KLRG1+ effector CD8+ cells that retain the expression of the transcription factor Bach2 (mainly CD127+ but not CD127− cells) are also capable of de-differentiating into KLRG1− memory cells with high functional capacity (Fig. 1) (12–14).

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Table 1. Phenotypes of T-cell subsets

	Naive	T_{MP}	T_{CM}	T_{EM} (T_{PM})	T_{RM}	T_{INF}	T_{EFF}	Prog T_{Ex}	Trans T_{Ex}	T_{RM} TIL	Term T_{Ex}
CD44		High	High	High	High	High	High	High	High	High	High
CD62L	+	−/+ [a]	+								
CCR7	+	−/+ [a]	+								
CD127	+	+	+								
CD28	+	−/+ [a]	+								
CD27	+	−/+ [a]	−/+ [a]	−/+ [a]							
TCF1	+	NA	+					+			
FOXO1	+	+	+	+	+ [a]	+		+			
CX3CR1				Int/High [a]	−/Int [a]	Int/High [a]	Int/High [a]		Int		
KLRG1				Int/High [a]		High	High		Int/High [a]	High [a]	
GzmB				Int/High [a]	High	Int/High [a]	High		High	High	
CD69					+ [a]			+	+	+	+
CD103					+ [a]					+	
P2RX7					+		+	NA	NA	+	+
TOX							Int	High	High	High	High
PD-1					High [a]	High [a]	Int	High	High	High	High
Tim-3					+ [a]	NA	+ [a]		+	+	+
CD101											+

GzmB, granzyme B; Int, intermediate; NA, not analyzed; Prog, progenitor; Term, terminal; Trans, transitory; T_{CM}, central memory T; T_{EFF}, effector T; T_{EM}, effector memory T; T_{EX}, exhausted T; T_{INF}, inflationary memory T; T_{MP}, memory precursor T; T_{PM}, peripheral memory T; T_{RM}, tissue-resident memory T; T_{RM} TIL, T_{RM}-like tumor-infiltrating lymphocyte. Blank indicates no or low expression.
[a]Depending on tissue and activation status.

In addition to effector versus memory differentiation, the strength of signaling also influences the types and numbers of memory T cells that are subsequently established. For instance, CD8+ T cells primed by antigen-presenting cells (APCs) with limited antigen cross-priming and co-stimulatory potential [e.g. CD11b+ dendritic cells (DCs)] tend to differentiate into central memory T (T_{CM}) cells that retain the expression of the LN homing receptors CCR7 and L-selectin (CD62L), and circulate in the lymph and blood (Table 1). In contrast, CD8+ T cells primed by APCs with stronger stimulatory potential (e.g. CD103+ DCs that express DNGR-1 and CD24, which potentiate enhanced cross-priming and co-stimulation, respectively) lose the expression of these receptors and differentiate into effector memory T (T_{EM}) cells that are maintained in the peripheral blood with occasional migration through the non-lymphoid tissues (15, 16). Recently, T_{EM} cells (CCR7− CD62L−) were further divided into two distinct sub-populations depending on their migratory properties and CX3CR1 expression: peripheral memory T (T_{PM}) cells that express intermediate levels of CX3CR1 ($CX3CR1^{int}$) and predominantly survey peripheral tissues, and T_{EM} cells that express high levels of CXCR1 ($CX3CR1^{hi}$) and lack the capacity to migrate to the peripheral tissues (thereby existing only in the blood) (17). Since the classical definition of T_{EM} cells (memory T cells that migrate between peripheral tissues and blood via lymph) is widely accepted and is identical to that of the newly classified T_{PM} cells, these populations are not actively distinguished in this review.

The functions of T_{EM} and T_{CM} cells differ significantly during a recall response to a secondary pathogen infection. T_{CM} cells respond by undergoing extensive proliferative and subsequent differentiation into effector cells. In contrast, T_{EM} cells exert immediate effector functions upon recall, but do not undergo extensive renewal (18–20). Furthermore, some cells that gain access to the peripheral tissues receive local microenvironmental cues that allow them to establish residency in the tissue and persist without recirculation. This localized population is referred to as tissue-resident memory T (T_{RM}) cells, and constitutes the major population of tissue memory. T_{RM} cells are a primary target of vaccination as these cells confer the first line of defense against re-infection (21). Accumulating evidence indicates that the trajectory of T cells into these distinct effector and memory T-cell subsets is highly regulated by their antigen experience and local environmental cues.

In this review, I outline the current understanding of how distinct activation signals program memory CD8+ T-cell differentiation and discuss options for improving vaccine strategies. Note the re-activation events described in this review refer to those induced during the primary response and not a recall response, unless otherwise stated.

Development of tissue-resident memory

Following the initial priming and activation event in the draining LNs (the first antigen hit), antigen-specific CD8+ T cells migrate to the site of infection (usually barrier tissues), where they eliminate pathogen-infected cells and ultimately die. During this process, a subset of effector CD8+ T cells (such as KLRG1− memory precursors) that arrive in the peripheral tissues receive environmental cues that direct their differentiation into T_{RM} cells (Fig. 1). Local tissue-derived environmental cues include cytokines, chemokines and other factors, such as TGF-β, IL-15, IL-7, IFN-α/β, TNF-α, IL-33, IL-12, IFN-γ, CCL5, CXCL10, CXCL12, CXCL16, Notch ligands, aryl hydrocarbon receptor (AhR) ligands and cognate antigen. Together, these factors co-operatively induce the acquisition of the TRM phenotype, enhance retention in the tissues, promote deposition into anatomical niches, improve the ability to exert effector functions, and prolong survival (21). Although

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Fig. 1. Contributions of antigen stimulation on the developmental path of CD8+ T cells. The ontogeny of T_{RM}-like TILs remains unknown. Black arrows indicate the antigen-independent differentiation paths. Red arrows indicate the antigen-driven differentiation paths and the thickness of the arrows indicates the strength of antigen signaling. Ad, adenovirus vector; Ag, antigen; CMV, cytomegalovirus; Flu, influenza virus; HIV, human immunodeficiency virus; LCMV, lymphocytic choriomeningitis virus; T_{CM}, central memory T; T_{EFF}, effector T; T_{EM}, effector memory T; T_{EX}, exhausted T; T_{INF}, inflationary memory T; T_{MP}, memory precursor T; T_{PM}, peripheral memory T; T_{RM}, tissue-resident memory T; TIL, tumor-infiltrating lymphocyte.

the specific array of instructive signals that drive T_{RM} formation differ in each tissue, cognate antigen-driven local activation always plays a central role (the second, and additional, antigen hits are termed as second hits hereafter) (21). Once established, CD8+ T_{RM} cells are maintained without recirculation and confer localized protection against re-infection.

A central mechanism by which effector (memory precursor) cells transition into long-lived T_{RM} cells is the enhanced retention (inhibition of egress from tissue) at the site of infection. This retention is driven by a second hit with antigen, which mediates the local up-regulation of the activation marker CD69 on the T cells (Table 1). CD69 antagonizes sphingosine-1-phosphate receptor 1 ($S1P_1$)-mediated egress from tissue, thereby promoting retention in tissue (22, 23). Antigen-independent bystander induction of CD69 expression or cytokine-induced down-regulation of Krüppel-like factor 2 (KLF2) and its transcriptional target $S1P_1$, can also promote the establishment of T_{RM} cells in remote barrier tissues (24–26). However, numerous studies have revealed that tissue retention is >50-fold more efficient when local antigen is present (27–29). Antigen-driven re-activation of T cells also leads to the expression of a T_{RM}-signature integrin CD103 that also promotes prolonged retention of the cells in the tissues (30). In addition to retention, TCR signaling also induces morphological changes in the cytoskeleton that promote trafficking through the basement membrane and into the epithelium (31) and *de novo* expression of chemokine receptors such as CXCR6 that sense chemokines expressed at the epithelium (32, 33).

Re-encounter with local antigen in barrier tissues also enforces regional protective immunity in both a T_{RM}-intrinsic and T_{RM}-extrinsic manner. During the acute phase of infection (when T_{RM} differentiation is initiated), CD8+ T_{RM} precursor cells compete with each other in recognizing cognate APCs at the site of infection, which results in the selection of T_{RM} cells with high-affinity TCRs and usually specific for dominant epitopes (34, 35). These T_{RM} cells retain a semi-activation status after the inflammatory response is over, and steady-state conditions have been established. This enables the cells to immediately secrete granzyme B and IFN-γ upon recall. These effector-like phenotypes of T_{RM} cells are observed in various mucosal tissues long after all evidence of cognate antigen has gone (24). Interestingly, however, the acquisition of immediate effector functions depends on the strength of local TCR signaling that the cell is exposed to in the tissues (because of the presence of persistent antigen depots). In this regard, CD8+ T_{RM} cells receiving stronger re-activation signals exhibit an enriched gene expression signature of effector functions than others (36, 37). This poised activation state of T_{RM} cells is maintained by the functional fitness of mitochondria and is regulated in part by a stress-responsive transcriptional factor, Bhlhe40, that is uniquely expressed in activated T_{RM} cells (38, 39).

Sustained up-regulation of various immune-checkpoint (IC) molecules, including programmed cell death-1 (PD-1) and T-cell immunoglobulin mucin-3 (Tim-3), is also evident on T_{RM} cells, implying the presence of cognate antigen-driven re-activation signals under steady-state conditions

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(Table 1) (40–44). Consistent with this, IC inhibitor (ICI) therapy (which blocks negative signals from, e.g. PD-1) significantly enhances the effector functions of CD8⁺ T_{RM} cells (45), highlighting the regulatory role of IC molecule signaling under steady-state conditions. Interestingly, these cells are not exhausted, as T_{RM} cells in most tissues remain functional, show distinct gene expression profiles from exhausted T cells and confer protection against re-infection (46). Since the blockade of interactions between PD-1 and PD-1 ligand 1 (PD-L1) after the resolution of primary infection significantly increases CD8⁺ T_{RM}-cell-mediated tissue damage and the development of fibrotic sequelae (45), it is likely that PD-1 expressed on CD8⁺ T_{RM} cells functions to inhibit unnecessary immune-mediated pathogenesis in tissues (47, 48).

Local re-activation also plays a role in the longevity of CD8⁺ T_{RM} cells. Early after infection, local re-activation of CD8⁺ T cells with cognate antigen in the barrier tissues leads to the up-regulation of the interferon-induced transmembrane protein 3 (IFITM3), a restriction factor that inhibits the entry and replication of various viruses, and protects T cells from infection-induced cellular dysfunction or death (49). Furthermore, recent studies have shown that P2RX7, a receptor that senses extracellular ATP (eATP), is highly, and selectively, expressed on CD103⁺ T_{RM} cells (Table 1) (50, 51). Although signaling via P2RX7 promotes the formation of T_{RM} cells by enhancing their metabolic fitness, excessive P2RX7 signaling in high eATP environments results in the selective death of T_{RM} cells. TCR signaling reduces P2RX7 expression on CD8⁺ T_{RM} cells, thereby protecting T_{RM} cells from danger signal-induced cell death (51). Since CD8⁺ T_{RM} cells preferentially localize at the site of tissue damage (22, 52), antigen-driven down-regulation of P2RX7 likely confers a survival advantage of antigen-specific T_{RM} cells over bystander T_{RM} cells.

It is currently unclear which cell types are the predominant APCs in the peripheral tissue microenvironment. Tissue DCs are the primary candidate, since targeted antigen delivery to this population facilitates the establishment of CD8⁺ T_{RM} cells (53). DCs that persist at the site of infection are also reported to provide the antigen-driven secondary signaling necessary for the functional maturation of effector CD8⁺ T cells during the early phase of infection (~day 5 post-infection) (54, 55). On the other hand, we and others have demonstrated a role for monocyte-derived macrophages in providing local antigen signaling at later phases of infection (around day 8–10 post-infection) (56–58). Lack of monocyte-derived macrophages, but not DCs, at this time point reduces the establishment of CD8⁺ T_{RM}, suggesting that tissue macrophages are a major APC in the peripheral tissues that facilitate the development of T_{RM} cells (58). This suggestion is supported by the fact that T_{RM} cells in various non-lymphoid tissues form clusters with macrophages under steady-state conditions (59–61). In addition to presenting antigen, monocyte-derived APCs also provide other necessary signals for optimal formation of T_{RM} cells, such as the glucocorticoid-induced TNFR-related protein ligand (GITRL) (57). Monocyte-derived APCs may be a provider of notch signaling, which improves the function and survival of T_{RM} cells by maintaining the transcription of the genes encoding IFN-γ and CD103 (43).

Advances in our understanding of local antigen in the establishment of T_{RM} cells in the peripheral tissues have been incorporated into novel vaccination strategies designed to promote barrier immunity. For example, topical delivery of chemokines or inflammatory stimuli promotes the recruitment of circulatory effector and memory T cells into the peripheral tissues, followed by the establishment of CD8⁺ T_{RM} cells even in the absence of cognate antigen, a strategy called 'prime and pull' (29, 62).

Importantly, a combination of the prime and pull strategy along with the topical administration of antigen results in a significant increase in the formation of CD8⁺ T_{RM} cells by inducing the local expansion of antigen-specific CD8⁺ T cells and recruiting new T_{RM} precursors, a strategy called 'prime–pull–amplify' (63, 64). This approach may be particularly effective in tissues where a simple prime and pull strategy is incapable of establishing CD8⁺ T_{RM} cells. For example, most CD8⁺ T cells recruited to the lung in response to antigen-independent inflammatory stimuli disappear after resolution of inflammation in the lung, but can be retained if there is also local administration of a small amount of antigen to this tissue (22, 28). In the liver, a strategy termed 'prime and trap' has been developed that involves targeted antigen presentation in the liver using an adenovirus vector. This approach efficiently traps circulating antigen-specific CD8⁺ T cells within the sinusoids and promotes T_{RM} formation (65). Hence, local antigen presentation offers exciting opportunities for enhancing site-specific deposition and amplification of antigen-specific CD8⁺ T_{RM} cells.

Development of memory-like T cells in chronic infection and cancer

During chronic infection and cancer, antigen-experienced CD8⁺ T cells are persistently exposed to high levels of cognate antigen in both lymphoid and non-lymphoid tissues. Chronic TCR stimulation leads to sustained up-regulation of multiple co-inhibitory IC molecules (e.g. PD-1, Tim-3, LAG3, CD38, CD39, CD160, TIGIT, 2B4 and CTLA4) that desensitize TCR signaling. Consequently, chronically stimulated T cells progressively lose effector functions, such as proliferative capacity, cytotoxicity and cytokine production and enter a state referred to as exhaustion (66). It should be noted here that not only dysfunctional cells, but also cells that differentiate into an exhausted state are termed as 'exhausted', irrespective of their functional capacities (Fig. 1). Various other factors, such as cytokines, immunoregulatory cells, the absence of CD4⁺ T-cell help, metabolic competition and tissue microenvironmental factors (stress signals, hypoxia, etc.) all contribute to the development and severity of T-cell exhaustion (67).

Antigen-driven signaling is the core mechanistic driver of exhaustion and, thus, antigen-specific CD8⁺ T-cell exhaustion predominantly occurs at the site of chronic infection or within the tumor (67, 68). It is now well appreciated that exhaustion is a unique, programmed differentiation state that prevents T cells from causing immunopathology in the presence of persistent antigen (69, 70) and from ultimate loss of antigen-specific T cells by activation-induced cell death (71, 72).

Exhausted CD8⁺ T cells are a heterologous population of cells that retain varying degrees of effector function and proliferative capacity. Functional differences between exhausted CD8⁺ T cells correlate with their differentiation stage. A small

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fraction of PD-1^{int} $CXCR5^+$ progenitor exhausted cells that express the transcription factor TCF1 and have self-renewal capability (also referred as to stem-like, memory-like, follicular cytotoxic or exhausted progenitor cells) are generated during the initial phase of exhaustion. In the presence of chronic antigen stimulation, $TCF1^+$ progenitor exhausted cells further differentiate into a transitory exhausted population that exhibit effector-like functional and transcriptional features ($TCF1^-$ PD-1^+ $CXCR5^-$ Tim-3^+ $CD101^-$ $CX3CR1^+$ granzyme B^{hi}) followed by the establishment of a large fraction of terminally exhausted cells lacking effector function ($TCF1^-$ PD-1^+ $CXCR5^-$ Tim-3^+ $CD101^+$ $CX3CR1^-$ granzyme B^{lo}) (Table 1 and Fig. 1) (73, 74).

$TCF1^+$ progenitor exhausted T cells sustain long-term anti-pathogen/tumor immunity by self-renewing and producing transitory exhausted cells, and are responsible for responding to ICI therapy, because of the generation of highly functional transitory exhausted cells (a process previously referred to as 're-invigoration' from dysfunctional states) (73, 74). $TCF1^+$ progenitor exhausted cells are considered as 'memory-like' based on the self-renewal capability as well as some phenotypic and transcriptional features (75–77), including sustained expression of the transcription factor FOXO1, necessary for memory survival and turnover (Table 1) (78, 79). However, it has become apparent that $TCF1^+$ progenitor exhausted cells are distinct from conventional 'memory' as the differentiation of effector/memory and exhausted cells branch relatively soon after priming (around day 7–8) (Fig. 1) (71, 80, 81).

Recent studies have demonstrated the crucial role of a transcription factor, TOX, in driving the exhausted differentiation program (71, 72, 82–84). Early after priming, cells that receive strong TCR signaling without adequate co-stimulation lack the NFAT binding partner AP-1 (a complex of Jun and Fos). Consequently, the activated TCR-responsive transcription factor NFAT in the absence of AP-1 induces multiple secondary transcription factors, including TOX and NR4A, which drive the exhaustion-related epigenetic program (84, 85). Although TOX is slightly up-regulated in $CD8^+$ T cells at the early phase of acute infection, high and sustained expression is specific to cells that develop exhaustion (82). Thus, exhausted $CD8^+$ T cells are not terminally differentiated descendants of effector cells. This notion is supported by the fact that $KLRG1^{hi}$ effector cells do not form exhausted T cells (82, 86).

Although the precise molecular requirements for the generation of $TCF1^+$ progenitor exhausted cells are not clear, preferential expression of CXCR5 and localization within the follicle in the secondary lymphoid tissues [as in the case of lymphocytic choriomeningitis virus (LCMV) clone 13 infection] suggests the supportive role of lymphoid structure in their development (87, 88). This may also explain the association of tertiary lymphoid structures with favorable responses to ICI therapy (89–91). Importantly, Jansen *et al*. have discovered a niche site where $TCF1^+$ progenitor exhausted cells are preferentially generated within the tumor. These cells reside in sites with dense accumulations of APCs (92). Furthermore, interactions with DCs within the tumor (second antigen hit) are required for the generation of optimal responses by tumor-reactive $CD8^+$ T cells upon ICI therapy (93). Thus, DC-mediated local priming or second hits within the tumor microenvironment may be beneficial for the generation and maintenance (by promoting self-renewal) of $TCF1^+$ progenitor exhausted cells and the acquisition of their effector function by providing optimal co-stimulatory signals (94).

In recent years, emerging evidence has indicated that some tumors, especially those of epithelial origin, harbor tumor-infiltrating lymphocytes (TILs) with T_{RM} characteristics (mainly determined by their expression of CD103 and CD69). These cells have been designated as 'T_{RM}' and their presence is associated with a favorable clinical outcome (95–97). It is important to note here that since tumor tissue is an 'antigen hot spot' where antigen-specific memory $CD8^+$ T cells re-encounter cognate antigen presented at high levels, differentiate into secondary effectors and exert effector functions, these cells are no longer stable 'memory' cells. Rather, high expression of multiple IC molecules as well as exhaustion-related transcriptome signatures suggests that these cells are in the state of exhaustion (98, 99). Therefore, we refer these cells as to 'T_{RM}-like TILs' to distinguish them from conventional T_{RM} cells (Fig. 1).

Comprehensive transcriptional profiling reveals that $CD8^+$ $CD103^+$ TILs exhibit a T_{RM}-like transcriptome signature, including transcripts related to enhanced tissue residency and up-regulation of adhesion as well as activation molecules (98, 100–102). $CD8^+$ $CD103^+$ T_{RM}-like TILs also show superior cytotoxic activity, compared with their $CD103^-$ counterparts, and express high levels of granzyme B, IFN-γ, TNF-α and perforin upon *in vitro* re-stimulation (98, 100, 103, 104). As with conventional T_{RM} cells described above, this enhanced cytotoxic activity is likely due to enhanced mitochondrial activity and high energetic potential (38, 105).

Furthermore, $CD8^+$ $CD103^+$ T_{RM}-like TILs represent a tumor-reactive cell population (98, 106) as these cells expresses high levels of IC molecules (e.g. PD-1, TIM-3, LAG3, TIGIT, CD39 and CTLA4) compared with their $CD103^-$ counterparts (98, 100, 101). Although some of these molecules are also expressed on conventional T_{RM} cells, the expression profile of other core exhaustion-associated genes on T_{RM}-like TILs is not enriched on conventional T_{RM} (Table 1) (48). This implies that T_{RM} and T_{RM}-like TILs diverge at a distinct differentiation branch: presumably at late to terminal stages of conventional effector/memory differentiation (T_{RM}) and an intermediate stage of exhausted differentiation (T_{RM}-like TILs) (Fig. 1). Importantly, $CD8^+$ $CD103^+$ T_{RM}-like TILs are also distinct from both $TCF1^+$ progenitor exhausted cells and transitory exhausted cells as $CD8^+$ $CD103^+$ T_{RM}-like TILs do not express TCF1, and constitute relatively large proportions of the $CD8^+$ TILs in some patients (~50–70%) (Table 1) (98, 100, 101). Thus, $CD8^+$ $CD103^+$ T_{RM}-like TILs represent a unique population of exhausted cells that retain high functional capacity (107).

Currently, little is known about the mechanisms by which $CD8^+$ $CD103^+$ T_{RM}-like TILs are generated within the tumor. As with conventional T_{RM} cells, tissue-derived instructive signals must drive differentiation into T_{RM}-like TILs since cells having T_{RM} characteristics are rarely found in the circulation. TGF-β in combination with TCR signaling is reported to be pivotal in the up-regulation of CD103 on $CD8^+$ TILs (105, 108). A role for TGF-β makes sense as TGF-β is considered to be an immunosuppressive factor that is produced at high levels in the tumor (109, 110). However, a question remains about

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why CD8+ CD103+ T_{RM}-like TILs maintain a strong cytotoxic potential, despite the presence of this suppressive cytokine.

One possible explanation is that TGF-β signaling promotes integrin inside-out signaling to activate CD103 via a Smad-independent pathway (111). This would enhance the co-stimulatory role of this integrin upon antigen re-activation of tumor-reactive CD8+ TILs within the tumor (103, 112). Alternatively, CD103 expression could be a surrogate marker of highly functional CD8+ TILs that infiltrated a less suppressive microenvironment (low external TGF-β) or were generated by yet-undefined mechanisms. This is supported by the fact that a large proportion of cancer-specific CD8+ CD103+ T_{RM}-like TILs can secrete and activate TGF-β, and continuously self-regulate CD103 expression without relying on the presence of external TGF-β (105).

Importantly, despite the frequent presence of CD8+ CD103+ T_{RM}-like TILs in human samples, these cells are not generated in traditional mouse tumor models. This limits opportunities to investigate the mechanisms by which these T_{RM}-like TILs are generated. Interestingly, Enamorado *et al.* have demonstrated that transfer of CD8+ T_{CM} into mice, followed by a tumor graft, resulted in the effective induction of CD8+ CD103+ T_{RM}-like TILs, suggesting that reprogramming of memory-fated cells within the tumor may be important (113). Accordingly, there is a need to further understand the biology of CD8+ CD103+ T_{RM}-like TILs.

Development of inflationary memory

Under physiological conditions where pathogens are completely eliminated, long-lived populations of memory T cells are established and persist in the absence of antigen. In the case of viruses that establish latency, such as cytomegalovirus (CMV), however, some CD8+ T cells with restricted specificities are continually re-exposed to latently expressed antigen. As a result, whereas most virus-specific CD8+ T-cell populations contract to form a stable central memory pool, CD8+ T cells specific for persistent antigens continue to expand and eventually stabilize at high frequency as memory cells with a distinct phenotype and functional profile, a process termed as memory T-cell inflation (114, 115). CD8+ T-cell pools exhibiting identical features with inflationary populations are also induced following infection with viruses that do not establish latency, such as replication-defective adenovirus vector (116, 117), polyomavirus (118) and parvovirus (119).

In the case of CMV, the virus establishes a lifelong latent infection (presence of static but ongoing gene expression in the absence of detectable virus), which is accompanied by intermittent viral re-activation (120). During this period, CD8+ T-cell responses are driven by epitopes that are occasionally but longitudinally presented, such as those derived from the immediate-early (IE) genes, which encode latent proteins necessary for initiating viral replication (121). Interestingly, both inflationary and non-inflationary epitopes are found within the same protein (121), implying that additional criteria, such as processing efficacy, the peptide affinity for MHC, the type of APC, the requirement for cross-presentation and co-stimulation, may be involved in the induction of inflation (115, 122). For example, whereas memory inflation is not compromised in the absence of the immunoproteasome (expressed selectively in professional APCs) (123), animals lacking antigen presentation on non-hematopoietic cells fail to induce inflationary responses (124), indicating the critical role of non-hematopoietic cells in CMV-mediated T-cell inflation. In this regard, the genetic deletion of CD28 has little impact on the induction of memory inflation (125), whereas other co-stimulatory molecules, such as 4-1BB and OX40, play an important role (126, 127). Although the salivary gland is known to be a major site of shedding and recrudescence of CMV, removal of this tissue does not impair memory inflation (128). Rather, the LNs have been found to be a primary site where virus-specific inflationary CD8+ T cells divide at a higher rate following CMV infection (129, 130). Thus, it is likely that non-hematopoietic cells in the LNs present latent epitopes.

In the case of immunization with replication-defective adenovirus vector, there is also evidence that some viral gene products are persistently presented for a long period (116, 131). This indicates that the long-term presentation of viral antigen, and not simply viral latency, is the key determinant for memory inflation. Adenovirus vector enters cells primarily via the cellular coxsackie/adenovirus receptor, which is expressed on a variety of cells and enables a broad tissue tropism (132). Thus, both hematopoietic and non-hematopoietic APCs co-operatively contribute to the induction and maintenance of memory inflation following immunization with adenovirus vectors and the specific site of inflation depends on the route of immunization (133)..

Whereas effector CD8+ T-cell populations specific for conventional (non-inflationary) epitopes contract and form stable memory with T_{CM} phenotypes (CCR7+, CD62L+, CD127+, CD28+, CD27+ and KLRG1−), CD8+ T cells specific for inflationary epitopes are repetitively exposed to antigen and undergo cell division at the site of antigen presentation under steady-state conditions. These cells exhibit phenotypical signs of activation (CCR7−, CD62L−, CD127−, CD28−, CD27− and KLRG1+) without undergoing rapid apoptosis, the characteristics of T_{EM} cells (Table 1) (114, 134, 135). It should be noted that while T_{EM} represent a memory cell population that is maintained in the absence of multiple antigen hits, the inflationary memory cells described in this review represent a memory cell population that has previously experienced re-activation-driven proliferation. Inflationary memory CD8+ T-cell populations are stable for more than a year post-infection depending on the continuous activity of FOXO1 (136), and their magnitude depends on the infectious dose (116, 137).

Importantly, however, adoptive transfer approaches have revealed that the half-life of expanded (inflationary) cells is shorter than that of conventional memory cells (estimated to be 45–60 days) (135). Thus, it has been proposed that inflationary memory pools are continuously replenished by newly expanded inflationary CD8+ T cells (135, 138). Recent thymic emigrants (naive CD8+ T cells) primed by persistent antigen are also involved in inflationary memory pools (135). However, these cells make only a minor contribution as thymectomy has essentially no impact on the maintenance of memory T-cell inflation (128). CD8+ T_{CM} cells are thought to be a major source of inflationary CD8+ T cells given their LN-surveying property and strong proliferative potential (Fig. 1) (115). As with exhausted CD8+ T-cell populations, it has become apparent that

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a small subset of TCF1⁺ T_{CM} cells are the source of inflationary CD8⁺ T cells (139). Re-activation driven down-regulation of CD62L induces a T_{CM} to 'T_{EM}-type' conversion and leads to the accumulation of inflationary CD8⁺ T cells in the blood and peripheral tissues (140).

Inflationary CD8⁺ T cells also lose the expression of CD27 and express intermediate levels of CX3CR1 upon re-activation (141), the characteristics of so-called 'peripheral memory' T cells (identical to the classical definition of T_{EM}) that circulate between peripheral tissues and blood (17). Although CX3CR1^{int} inflationary CD8⁺ T cells still retain their proliferative capacity, excessive re-activation (e.g. high-dose infection) induces progressive differentiation into CX3CR1^{hi} cells that have a relatively weak capacity for self-renewal and tissue surveillance (17, 137, 141). Furthermore, when inflationary CD8⁺ T cells (CX3CR1^{int}) are recruited to the peripheral tissues, some of them acquire the characteristics of T_{RM} calls and persist without recirculation, although the efficacy of the T_{EM}-type to T_{RM} conversion is limited even in the presence of local antigen (e.g. in the salivary gland where CMV sporadically recurs) (140, 142, 143).

In contrast, we and others have found that local administration of inflation-inducing pathogens results in the long-term presentation of pathogen antigens in mucosal tissues. CD8⁺ T_{EM} cells that survey these peripheral tissues are continuously activated by locally presented antigens, undergo proliferation without rapid apoptosis, and acquire T_{RM} phenotypes and longevity. We termed the continuous local antigen-driven T_{EM} to T_{RM} conversion and proliferation in the mucosal tissues as 'T_{RM} inflation' (144–146). Although the molecular requirements for the induction of T_{RM} inflation and detailed characteristics of inflationary T_{RM} cells still remain unclear, CX3CR1^{int} cells with a high proliferative potential, but not CX3CR1^{hi} cells, may be a source of inflation. It will be important to identify the mechanisms underlying T_{RM} inflation in future studies.

Sustained effector functionality without the features of exhaustion is a defining feature of inflationary memory. For example, the expression of PD-1 is not elevated on inflationary CD8⁺ T cells, despite repetitive antigen exposure (135). One possible explanation is that the strength and frequency of re-stimulation events that induce memory inflation are weaker than those that induce exhaustion (147). However, this fails to explain why T_{RM} cells (which are assumed to receive weak re-stimulatory signals) express PD-1, but inflationary memory T cells do not. It is possible that since inflationary memory T cells preferentially develop during the later phase of infection, the low expression of IC molecules on inflationary memory cells may reflect the lack of excessive inflammatory signals induced during the onset of infection (T_{RM} cells potentially receive these signals because of the presence of continuous exposure of environmental contaminants from outside the body).

The differential impact of inflammatory signals during the onset and late phase of infection is also observed in chronically infected animals. For example, antigen-specific CD8⁺ T cells primed at the late phase of LCMV clone 13 infection are less exhausted, preferentially express TCF1 and respond better to immunotherapy (75). Another interpretation would be that the expression of IC molecules may be up-regulated upon re-activation, but are subsequently down-regulated when the cells enter the circulation. This possibility remains an open question since there are no published data regarding PD-1 expression on inflationary memory T cells at the site of re-activation (147).

It is important to note here that a key difference between inflationary memory and other T-cell populations that are repetitively exposed to antigen (T_{RM} and exhausted cells) is that the former do not stay at the site of re-activation and circulate throughout the body, which presumably avoids antigen-driven overstimulation and sustained up-regulation of IC molecules. This notion is supported by our observation that the induction of memory inflation in the lung resulted in the accumulation of inflationary memory CD8⁺ T cells in the lung that highly express PD-1 (146). It is clearly of interest to identify the mechanisms by which locally inflamed CD8⁺ T cells maintain their functionality, even in the presence of persistent antigen.

Conclusions and future perspective

Antigen-driven re-activation is a crucial decision point in the differentiation of antigen-experienced CD8⁺ T cells. Optimal levels of antigen signaling confer various *de novo* instructions, such as to stay at the site of re-activation, to migrate to newly accessible sites by altering the expression of chemokine receptors and adhesion molecules or to maintain the poised state of activation that accelerates effector functions upon recall. It is important to note here that re-activation may not always be induced by a single interaction of CD8⁺ T cells with APCs. For example, in the case of T_{RM} formation at the epithelium, it is possible that cells experience multiple antigen hits (for example, both in the parenchymal stroma and the epithelial layer). Multiple hits may also drive the production of inflationary CD8⁺ T cells and their functional diversity, such as CX3CR1^{int} cells that still retain proliferative capacity and CX3CR1^{hi} cells that are highly activated and exhibit a limited self-renewal capacity. A similar mechanism (number of hits corresponding to progressive differentiation) may also regulate the different levels of T-cell exhaustion. Although a high level of persistent antigen presentation is detrimental to the elaboration of effector functions by memory CD8⁺ T cells, it is to an extent fine-turned to maintain a host–pathogen stalemate by controlling the outgrowth of chronically infected pathogens while preventing the immunopathology associated with prolonged effector functions.

There are no primary studies that directly compare the nature of antigen presentation that promotes T-cell differentiation into T_{RM} cells, inflationary memory and exhausted populations. Available data on phenotypic, transcriptional and epigenetic profiles have suggested that the quality, and quantity, of antigen signaling is associated with the development of these populations (147–149). As discussed above, however, a limitation is that most inflationary memory cells are sampled from the peripheral blood or spleen, long after their re-activation, whereas T_{RM} and exhausted cells are sampled after recent re-activation.

Even among recently re-activated cells, the antigen signals that induce T_{RM} formation (described as the second hit during the acute phase of infection) and re-activation (sustaining the activation status of T_{RM} cells under steady-state conditions) also differ significantly. In the latter case, re-activation is induced by so-called 'residual antigen'

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or via an 'antigen depot', which is usually located at the site of infection and draining LNs for several months after clearance of acutely infectious pathogens (150–153). Although re-activation with residual antigen in the LNs promotes basal recruitment of circulatory memory to the non-lymphoid tissues by inducing T_{CM} to T_{EM} conversion without apparent proliferation (151, 153), such antigen presentation in the peripheral tissues does not promote T_{RM} formation, suggesting relatively weaker stimulatory capacity (Fig. 1) (32). In contrast, as described above, local antigen presentation induced by latent virus infection can convert T_{EM} to T_{RM} cells at basal levels during the late phase of infection (142, 143), implying a stronger stimulatory potential compared with residual antigen.

Thus, it will be important to compare re-activated cells in the context of optimal time courses and in the optimal tissues. Furthermore, in these cases, a fundamental question is why APCs bearing cognate antigen are not fully eliminated, even in the presence of functional memory $CD8^+$ T cells. Although the contribution of PD-1-mediated basal levels of suppression (less than that needed to induce exhaustion) is strongly suspected, there could be alternative mechanisms to evade $CD8^+$ T-cell-mediated cytolysis (154).

Taken together, the antigen signals that regulate the establishment and maintenance of distinct memory subsets differ spatially and temporally. A comprehensive understanding of the nature and timing of antigen presentation in each tissue is essential to develop vaccination strategies that generate optimal memory $CD8^+$ T-cell subsets in the desired tissues.

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