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Impact of inflammatory cytokines on effector and memory CD8+ T cells

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Inflammatory cytokines have long been recognized to produce potent APCs to elicit robust T cell responses for protective immunity. The impact of inflammatory cytokine signaling directly on T cells, however, has only recently been appreciated. Although much remains to be learned, the CD8 T cell field has made considerable strides in understanding the effects of inflammatory cytokines throughout the CD8 T cell response. Key findings first identified IL-12 and type I interferons as "signal 3" cytokines, emphasizing their importance in generating optimal CD8 T cell responses. Separate investigations revealed another inflammatory cytokine, IL-15, to play a critical role in memory CD8 T cell maintenance. These early studies highlighted potential regulators of CD8 T cells, but were unable to provide mechanistic insight into how these inflammatory cytokines enhanced CD8 T cell-mediated immunity. Here, we describe the mechanistic advances that have been made in our lab regarding the role of "signal 3" cytokines and IL-15 in optimizing effector and memory CD8 T cell number and function. Furthermore, we assess initial progress on the role of cytokines, such as TGF-β, in generation of recently described resident memory CD8 T cell populations.

Keywords: signal 3, cytokines, effector, resident memory, memory, CD8 T cells

INTRODUCTION

Naïve CD8 T cells undergo activation when presented with their cognate antigen following a three-signal model. Professional antigen-presenting cells (APCs) provide the crucial first and second signals through the T cell receptor (TCR) and costimulatory molecules, while innate immune cells contribute inflammatory cytokines to promote optimal accumulation and differentiation of effector CD8 T cells (1). Although the role of inflammatory cytokines in maturing professional APCs to stimulate robust T cell responses has been well described (2), investigation of their direct effect on T cells is ongoing. In the following review, we outline mechanistic studies identified for inflammatory cytokine regulation of various stages of the CD8 T cell response and discuss cutting edge research on the cytokine requirements for generation of the novel resident memory T cell (T_{RM}) population.

SIGNAL 3 CYTOKINES AND THE MAGNITUDE OF THE EFFECTOR CD8 T CELL RESPONSE

Initial studies suggesting that cytokines, particularly IL-12, may be important for signaling directly to T cells were made in *in vitro* cultures of T cells and artificial APCs more than a decade ago. Since then, the importance of IL-12 and type I interferon signaling directly to CD8 T cells for optimal effector cell accumulation has been demonstrated both *in vitro* and *in vivo* (3–7). Despite the clear impact of IL-12 and IFNα/β on effector CD8 T cell numbers, it remained unclear how inflammatory cytokines regulated the magnitude of effector CD8 T cell responses. Although several other cytokines have been discussed in the literature recently for T cell differentiation (8, 9); here, we will focus on signal 3 cytokines as originally defined for their role in T cell accumulation (3–7). After their classification as signal 3 cytokines, IL-12 and type I interferons were proposed to enhance accumulation of CD8 T cells following one of two models: via greater survival (2, 10) or by conferring an early proliferative advantage (11, 12). The model for enhanced survival stemmed from 3 days culture experiments, which demonstrated accumulations of cells in cultures containing IL-12 with no detectable changes in cell division. The latter model was supported also by *in vitro* studies, where IL-12 transiently increased expression of CD25, the high affinity IL-2 receptor, peaking at day 2 (11). Hence, previous reports addressing the mechanism by which signal 3 cytokines allow optimal accumulation of effector CD8 T cells were limited to short-term *in vitro* experiments with no clear answer to the question of whether survival or early proliferation, or both, contribute to the magnitude of the CD8 T cell response. Furthermore, the temporal disconnect between signal 3 cytokine-driven CD25 expression and optimal accumulation of effector CD8 T cells many days later has not been assessed (13). Here, we describe a recent study from our lab addressing these knowledge gaps concerning the mechanism by which signal 3 cytokines allow optimal accumulation of effector CD8 T cells *in vivo*.

Utilizing an OT-I T cell adoptive transfer system followed by DC-OVA priming with or without the TLR9 agonist, CpG, to induce signal 3 cytokines, Starbeck-Miller et al. compared CD8 T cells activated *in vivo* in the presence or absence of signal 3 cytokines (14). Gene expression profiling of T cells from these groups at D7 post immunization clearly showed that signal 3 cytokines enhanced transcription of proliferation, but not

anti-apoptosis-associated genes (14). Additionally, analysis of CD8 T cells primed by DC with or without signal 3 showed no differences in proliferation or total cells numbers as late as day 5 post immunization. Thus, the *in vivo* data do not support either of the proposed models for signal 3 activity. Interestingly, both DC and DC + CpG OT-I cells isolated on D4 and moved into *in vitro* cultures failed to divide, although transfer of the same populations to an *in vivo* host revealed more robust proliferation from the CD8 T cells that had been exposed to signal 3 cytokines. This suggested that signal 3 cytokines established a proliferation program, but sustained proliferation required an additional component that was present in a naïve host. Since IL-2 is an important driver of T cell accumulation, Starbeck-Miller et al. monitored expression of the high affinity IL-2 receptor, CD25, on DC versus DC + CpG CD8 T cells. Indeed, IL-12 and type I interferon sustained CD25 expression, allowing for greater IL-2-induced proliferation via activation of the PI3K pathway and expression of FoxM1, a positive cell cycle gene regulator. Importantly, administering the IL-2 neutralizing antibody JES6 from D4-6 removed the proliferative advantage conferred by signal 3 cytokines. Thus, these studies verify, and add mechanistic insight to the model, indicating that signal 3 cytokines neither enhance survival not provide and early proliferative advantage, but rather sustain expression of the high affinity IL-2 receptor, which extends the duration of proliferation after immunization and permits optimal generation of effector CD8 T cells *in vivo.* Interestingly, the effects of IL-12 and type I interferons are not limited to promoting optimal CD8 T cell accumulation, but offer functional advantages to effector CD8 T cells, such as antigen sensitivity, which will be discussed next.

DYNAMIC REGULATION OF ANTIGEN SENSITIVITY BY INFLAMMATORY CYTOKINES

The protective capacity of CD8 T cells depends on their quantity, functional properties, and anatomical distribution (15). High antigen sensitivity, otherwise referred to as functional avidity, strongly correlates with protective immunity against intracellular pathogens (16). Although T cells cannot directly alter the binding affinity of their TCR through processes like somatic hypermutation, it has been shown that monoclonal TCR-transgenic CD8 T cells can increase their functional avidity from early to late effector time points (17). This study suggested that the functional avidity maturation was a fixed property of CD8 T cells. Here, we describe a mechanistic study demonstrating that inflammatory cytokines directly enhance antigen sensitivity of effector and memory CD8 T cells, however this enhanced sensitivity is not hardwired, but rather tuned by the pathogen-specific milieu.

Using a similar DC immunization protocol as indicated previously, Richer et al. activated OT-I CD8 T cells in the presence or absence of signal 3 cytokines (18). Distinct inflammatory milieu were then initiated by co-infection of DC primed mice with *Listeria monocytogenes* (Lm) or lymphocytic choriomeningitis virus (LCMV) and antigen sensitivity was assessed at day 5 after priming. Strikingly, DC-OVA with LCMV infection substantially enhanced antigen sensitivity by more than 10-fold whereas co-infection with Lm enhanced antigen-sensitivity four to six-fold. To determine whether inflammation increased functional avidity via enhanced TCR signaling, Richer et al. isolated OT-I T cells from DC and DC + LCMV mice on D4 and analyzed phosphorylation of downstream TCR signals after TCR ligation (18). Indeed, inflammatory cytokines dramatically enhanced phosphorylation of ZAP-70, PLCgamma, and ERK1/2 in response to TCR stimulation. Importantly, greater ERK1/2 phosphorylation was not observed with PMA stimulation, which bypasses proximal TCR signals, suggesting that inflammatory cytokines increased the antigen sensitivity of the TCR by enhancing proximal TCR signaling. Consistent with the data from effector CD8 T cells, inflammatory cytokines also increased the antigen sensitivity of memory CD8 T cells by enhancing TCR proximal signaling, albeit to a lesser degree than observed with effector CD8 T cells. This study demonstrated how the pathogen-specific inflammatory milieu affects antigen-sensitivity, an essential functional aspect of both effector and memory CD8 T cells. In addition to signal 3 cytokine effects on memory CD8 T cells, we next review a novel role for IL-15 in memory CD8 T cell trafficking.

IL-15-DEPENDENT SYNTHESIS OF SELECTIN LIGANDS

Numerous studies have described the functional differences between memory and naïve CD8 T cells (13, 19). Among such reports, it was demonstrated that memory, but not naïve, CD8 T cells can be rapidly recruited to inflamed lungs in an antigen-independent manner (20). Importantly, this large influx of memory CD8 T cells was shown to provide immediate cytolytic killing against pathogens expressing cognate antigen (21). Although this non-specific recruitment of memory CD8 T cells was shown to depend on CCR5 expression, the molecular mechanisms initiating early "tethering and rolling" events before chemokine recognition by memory CD8 T cells detection remained undefined.

Immune cell homing is a highly regulated process that begins with selectin family proteins. Leukocytes extravasate into inflamed tissue by constructing ligands to P- and E-selectin, which are expressed on activated endothelium. In contrast, L-selectin mediates homeostatic trafficking of naïve and central memory CD8 T cells through lymph nodes. Previous reports concerning the synthesis of P- and E-selectin ligands had been limited to *in vitro* models, which suggested TCR activation was essential to express appropriate selectin ligands. Herein, we describe studies from Nolz et al. that show P- and E-selectin ligand synthesis occurs on memory, but not naïve, CD8 T cells following inflammation *in vivo* (22). Utilizing the model pathogen, LCMV, Nolz et al. observed uniform expression of functional P- and E-selectin ligands on effector populations, but that most memory CD8 T cells did not express functional P or E-selectin ligands. After detecting high selectin ligand expression on non-specifically recruited memory P14 CD8 T cells following several irrelevant pathogen infections, it was demonstrated, through use of blocking antibodies to P- and E-selectin or P-selectin glycoprotein ligand-1, that non-specific recruitment of memory CD8 T cells to inflamed sites was dependent on selectin binding. To investigate the mechanism regulating inflammation-induced selectin ligand expression on memory CD8 T cells, Nolz et al. analyzed expression of the *Gcnt1* gene, which prompts their formation on naïve, effector, and memory CD8 T cells. Although effector CD8 T

cells expressed high levels of *Gcnt1*, naïve, and memory CD8 T cells had minimal expression of this protein. Interestingly, recombinant IL-15 substantially enhanced P- and E-selectin ligand synthesis on memory, but not naive CD8 T cells *in vitro* and Nolz et al. revealed a similar induction of the Gcnt1 protein via immunoblot. *In vivo*, IL-15-deficiency significantly reduced expression of selectin ligands, and subsequent memory CD8 T cell trafficking to inflamed sites, suggesting that P- and E-selectin ligand expression occurs in an IL-15/STAT5-dependent, but TCR-independent manner. Importantly, IL-15-driven P- and E-selectin ligand expression was shown to occur in human memory CD8 T cells, demonstrating conserved trafficking pathways between mouse and human T cells that can be manipulated for therapeutic purposes.

Until now, IL-15 has been referred to, principally, as a maintenance cytokine for memory CD8 T cells. This study investigating the role of IL-15 in the regulation of core 2 O-glycan synthesis on memory CD8 T cells suggests the possibility of other unexplored functions of this important inflammatory cytokine.

TGF-β, IL-33, AND TNF REQUIRED FOR RESIDENT MEMORY CD8 T CELLS

Although the CD8 T cell field has established a paradigm of IL-15-driven homeostatic proliferation as the model of memory CD8 T cell maintenance for circulating T cells, localized CD8 T cell populations in the lung (23), gut (24), and skin (25), among other tissues, have been shown to sustain a sizable pool of memory CD8 T cells despite the absence of IL-15 signaling. Most recently, the T_{RM} population has garnered immense interest for their distinct surface phenotype, local protective capacity, and long-term maintenance in the absence of traditional cytokines. Skin and gut infection models to generate transgenic CD8+ T_{RM} populations are well established (26, 27); hence, we describe recent advances in determining the cytokine signals involved for T_{RM} development and maintenance following either immunization or infection.

Resident memory T cell cells represent a novel, non-circulating class of T cells that persist within extralymphoid tissue and demonstrate superior regional immunity (28). The best-characterized T_{RM} cells express the alpha chain of the αEβ7 integrin (CD103), as well as the sphingosine 1 phosphate receptor ($S1PR_1$) inhibitor CD69, in multiple tissue compartments. Relevantly, both molecules are required for the optimal formation and maintenance of T_{RM} cells in the skin (26). Since *in vitro* and some *in vivo* studies have long since shown that transforming growth factor-β (TGF-β) signaling promotes CD103 expression on immune cells (29–31) and that TGF-β is expressed in the skin epithelium, Mackay et al. investigated whether signaling through the TGF-β receptor was required to upregulate CD103 and establish T_{RM} cells *in vivo* (26, 32). Utilizing one to one adoptive transfer models of WT and *Tgfbr2*$^{f/f}$.dLck-Cre (Tgfbr2−/−) OT-I T cells into C57BL/6 mice followed by infection with OVA-expressing HSV, Mackay et al. indeed demonstrated that Tgfbr2−/− OT-I cells failed to upregulate CD103 and had a dramatically reduced ability to form T_{RM}.

By utilizing acute and chronic infections with LCMV, Zhang et al. delved further into the mechanism behind TGF-β signaling for generation and maintenance of T_{RM} cells (27). Creating equal ratio mixtures of WT and Tgfbr2−/− P14 T cells followed by either LCMV-Armstrong (acute) or Clone 13 (Cl13, chronic) infections, Zhang et al. notices defective maintenance of Tgfbr2−/− cells in Armstrong, but not Cl13-infected hosts. While monitoring integrin expression in secondary lymphoid organs, which are the major source for T_{RM} cells, Zhang et al. detected enhanced expression of α4β7 on Tgfbr2−/− cells in Cl13, compared to Armstrong-infected mice (27). As α4β7 aids in the migration to the gut (33, 34), it was concluded that, although Tgfbr2−/− T_{RM} cells are locally declining in both Armstrong and Cl13-infected mice, the more prominent, enhanced expression of α4β7 on splenic Tgfbr2−/− T cells of Cl13-infected hosts allowed for continual replacement and stabilization of T_{RM} numbers. Thus, TGF-β acts as a negative regulator to T_{RM} formation through α4β7 downregulation, but is required for the maintenance of established T_{RM} cells in the gut through induction of CD103 expression.

The above findings clearly identify the relationship between TGF-β and CD103 expression for persistence of T_{RM} cells; however, CD103 is not required in all T_{RM} niches (35–37). Thus, we outline a complementary study, defining the transcriptional regulation of a ubiquitous T_{RM} marker, CD69, to establish T_{RM} cells, where CD103 may be dispensable. The antagonistic relationship between CD69 and $S1PR_1$ are well established (38). The zinc-finger transcription factor KLF2 catalyzes the expression of $S1PR_1$, known to promote lymph node egress (39). Hence, Skon et al. initially uses adoptive transfer models of KLF2-GFP P14 T cells followed by LCMV-Armstrong infection to monitor KLF2 expression in circulating, compared to resident memory CD8 T cells (40). As expected, T_{RM} cells expressed low levels of both KLF2 and $S1PR_1$, while CD69 expression was increased. Interestingly, *in vitro* cytokine screening revealed that a combination of TGF-β, IL-33, and TNF were capable of inducing a modest downregulation of KLF2 expression. To analyze the effect of $S1PR_1$ expression on T_{RM} formation, Skon et al. overexpressed $S1PR_1$ through retroviral transduction of P14 cells, and demonstrated that failure to downregulate $S1PR_1$ prevented the establishment of T_{RM} cells in the salivary gland, kidney, lamina propria, and intestinal epithelium (40). Hence, these studies propose that migration to non-lymphoid tissue enhances exposure of CD8 T cells to TGF-β, IL-33, and TNF, which triggers some loss of KLF2 expression, subsequently decreasing $S1PR_1$, and allowing CD69 upregulation. Although the upregulation of CD69 may be controlled by multiple factors, increasing the complexity of this process, these studies, among others, clearly demonstrate that the non-migratory T_{RM} population has novel cytokine requirements for their generation and maintenance (**Figure 1**) and that this list of cytokines may continue to expand.

SYNOPSIS

In this review, we outline recent studies uncovering the mechanisms by which inflammatory cytokines regulate various attributes of circulating and resident memory CD8 T cell populations. Although investigation of the role of inflammatory cytokines on T_{RM} cells, and T cells in general, remain far from complete, the field

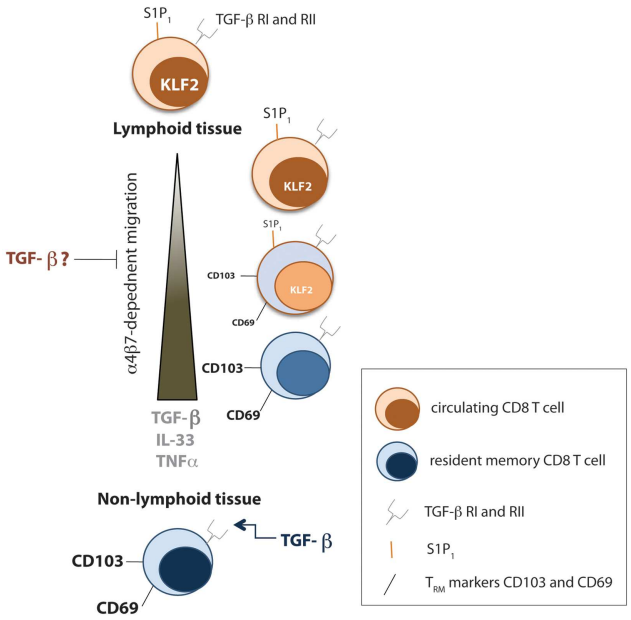

FIGURE 1 | Cytokines involved in TRM formation and maintenance. Early after infection, local TGF-β signals prevent migration of effector CD8 T cells from the spleen to non-lymphoid tissue by downregulating the αEb7 integrin. However, tissue-specific programming during priming of CD8 T cells causes homing to appropriate resident tissue. In addition, the transcription factor KLF2 gets downregulated as effector CD8 T cells travel to non-lymphoid tissue toward a combination of TGF-β, IL-33, and TNFα signals, which causes a decrease in S1P1, allowing upregulation of CD69. Within resident tissue, TGF-β signals sustain TRM numbers.

has made remarkable progress in understanding how the inflammatory environment can directly modulate the number, function, migration, and maintenance of T cells.

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