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The multifaceted role of CD4+ T cells in the regulation of CD8+ T cell memory maturation

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Abstract

Following infection, T cells differentiate into a heterogeneous population of effector T cells that can mediate pathogen clearance. A subset of these effector T cells possesses the ability to survive long-term and mature into memory T cells capable of providing long-term immunity. Understanding the signals that regulate the development of memory T cells is crucial to efforts to design vaccines capable of eliciting T cell-based immunity. $CD4^+$ T cells are essential for the formation of protective memory $CD8^+$ T cells following infection or immunization. However, until recently, the mechanisms by which $CD4^+$ T cells act to support memory $CD8^+$ T cell development following infection were unclear. Here, we discuss recent studies that provide insight into the multifaceted role of $CD4^+$ T cells in the regulation of memory $CD8^+$ T cell differentiation.

Memory $CD8^+$ T cells are a principal component of immunity against intracellular pathogens such as viruses. They are distinguished by their capacity to survive long-term and undergo rapid and robust proliferation and acquisition of effector function upon antigen re-exposure [1]. Memory $CD8^+$ T cells can vary in their phenotype, localization, and function allowing them to protect the host against a broad array of potential insults. $CD8^+$ T cells can mediate the killing of infected cells through multiple mechanisms including expression of granzymes and perforin, as well as the secretion of cytokines such as interferon γ (IFN γ) and tumor necrosis factor α (TNFα). Unlike neutralizing antibodies that largely recognize proteins expressed on pathogen surfaces, $CD8^+$ T cells respond to peptide sequences presented on the surface of antigen presenting cells. This allows them to recognize internal proteins of the pathogen that are less subject to evolutionary pressure and thus tend to be more highly conserved among different pathogen variants. Therefore, $CD8^+$ T cells possess the potential to provide broadly reactive protection against viruses such as influenza or HIV that rapidly mutate their surface proteins [2].

Despite the utility of memory $CD8^+$ T cells in protection against pathogens that rapidly mutate to elude neutralizing antibodies, the development of T cell based vaccines has proven

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problematic [3]. This failure is largely due to an incomplete understanding of the signals and cell types that operate at different stages of the immune response to influence the quantity and quality of developing memory $CD8^+$ T cells. Additionally, knowledge of how $CD8^+$ T cells are able to enter and maintain residence in mucosal tissues is of critical importance as many of the infections to which effective vaccines have not been developed initially infect mucosal sites such as the lungs, reproductive tract, and skin. In order to generate a protective memory $CD8^+$ T cell response it is important to understand the signals needed to position them at the initial site of infection, as well as to induce a circulating memory pool capable of preventing outgrowth of the pathogen.

The T cell response to acute infection can typically be divided into three phases —priming and expansion, resolution and contraction, and memory. During the first phase, naïve $CD8^+$ T cells divide and differentiate into effector cells that acquire the ability to produce IFNγ, TNFα and cytotoxic proteins such as granzymes and perforin [4]. Following viral clearance, contraction and resolution ensues in which the majority of the effector $CD8^+$ T cells die with ~5–10% surviving. These enter the third stage — the 'memory' phase — and are maintained long-term by signals such as IL-7 and IL-15 [5]. While considerable heterogeneity exists among long-lived $CD8^+$ T cells, they are typically divided into resident (T_{RM}), effector (T_{EM}), and central (T_{CM}) memory cells. Differences in their localization, recall ability, and effector functions allow them to provide overlapping layers of protection against potential reinfection [6]. T_{RM} cells are located in mucosal sites such as the lungs, skin, and reproductive tract and are unique from other memory populations in that they do not reenter the circulation. They are characterized by high expression of CD103 and CD69 and act as sentinels to provide immediate protection upon local secondary infection through direct effector functions and the recruitment and reactivation of immune cells [7–12]. The developmental pathway and function of T_{RM} cells are reviewed elsewhere in this issue. [Cite Mackay, Mueller review] T_{EM} cells can migrate between tissues and secondary lymphoid organs and provide immune surveillance. T_{EM} cells have constitutive expression of some effector functions and lack expression of L-selectin (CD62L) and CCR7 [5]. T_{CM} cells reside in secondary lymphoid organs and are typically characterized by expression of these molecules needed for entry therein. They possess the greatest proliferative potential among the memory T cell subsets and can rapidly expand and differentiate following rechallenge.

Considerable work over the past decade has sought to elucidate the signaling and transcriptional networks governing $CD8^+$ T cell fate decisions, with these studies reviewed recently [5]. This Review will focus on the essential role of $CD4^+$ T cells in the development of memory $CD8^+$ T cells [13–19]. They regulate $CD8^+$ T cell memory development through multiple mechanisms, depending on the type of infection or immunization [20]. Here we will discuss recent studies that provide mechanistic insight into the process underlying the necessity of $CD4^+$ T cells in memory $CD8^+$ T cell maturation and function in different settings.

$CD4^+$ T cell help following immunization

Following immunization, $CD4^+$ T cells are necessary for the induction of a robust primary $CD8^+$ T cell response (Fig. 1a)[21–28]. Additionally, $CD8^+$ T cells formed in the absence of

CD4$^+$ T cell help are impaired in their long-term maintenance and display poor proliferative ability upon secondary challenge [13,16,29,30]. Considerable work has sought to understand the processes underlying these defects.

A primary mechanism by which CD4$^+$ T cells support the CD8$^+$ T cell response following immunization is through the "licensing" of dendritic cells (DCs). CD4$^+$ T cell help is required for DCs to increase their antigen-presentation and co-stimulatory capacity to levels sufficient to induce a robust effector CD8$^+$ T cell response, with both the CD4$^+$ and CD8$^+$ T cells recognizing antigen presented by the same DC [22]. This licensing is mediated through CD40: CD40L interactions between the DC and cognate CD4$^+$ T cell that allow for the functional maturation of DCs [21,24]. The licensed DCs can subsequently interact with CD8$^+$ T cells and induce a strong primary response [23]. In some settings, CD40: CD40L interactions can also occur directly between CD8$^+$ T cells and CD4$^+$ T cells [16].

CD4$^+$ T cells also can support the primary CD8$^+$ T cell response through facilitation of their interaction with DCs. Prior to antigen encounter, CD8$^+$ T cells in the draining lymph node (dLN) upregulate the chemokine receptor CCR5. These cells can then migrate towards the site of antigen-specific DC: CD4$^+$ T cell interactions due to the production of chemokines such as CCL3 and CCL4 by the licensed DCs [31]. This guidance of naïve CD8$^+$ T cells provides an explanation for how they can rapidly find their cognate antigen-presenting cell following immunization, despite the low frequency of both of these populations. CD4$^+$ T cells licensing of DCs also can facilitate entry of naïve CD8$^+$ T cells into the dLN through expansion of the arteriole feeding the dLN, as well as enlargement of the dLN itself, although the precise mechanism by which CD4$^+$ T cells regulate this process remains to be determined [32].

Further insight was provided by two recent studies evaluating the spatiotemporal interactions of DCs and cognate T cells [33,34]. One found that CD4$^+$ T cell activation precedes that of CD8$^+$ T cells and occurs through interactions with migratory DCs [34]. Activated CD4$^+$ T cells upregulate CD40L and subsequently license cross-presenting XCR1$^+$ DCs that can engage and activate antigen-specific CD8$^+$ T cells [34]. A separate study found that both CD4$^+$ and CD8$^+$ T cells are activated by distinct DC subsets (non-infected and infected DCs, respectively) at separate anatomical locations [33]. These activated T cells then interact with cognate XCR1$^+$ DCs in clusters, which act as the platform by which CD4$^+$ T cell help is provided to the CD8$^+$ T cells [33]. Going forward it will be important to clarify differences between these and previous works regarding whether CD8$^+$ T cells are activated by distinct DCs prior to engagement with XCR1$^+$ DCs, and if initial engagement of CD8$^+$ T cells with XCR1$^+$ DCs precedes licensing of these DCs by CD40L-expressing CD4$^+$ T cells or whether theses interactions occur simultaneously.

In addition to their role in the primary response, CD4$^+$ T cells are necessary for robust secondary expansion of memory CD8$^+$ T cells [13,16,27,29,30,35,36]. One suggested mechanism for this requirement is through regulation of tumor-necrosis factor-related apoptosis-induced ligand (TRAIL) [37,38]. "Helpless" CD8$^+$ T cells rapidly induce TRAIL expression upon restimulation and undergo activation-induced cell death, although TRAIL deficiency does not seem to rescue secondary responsiveness of "helpless" cells in all settings [30]. The ability

of $CD8^+$ T cells to respond upon secondary challenge appears to be imprinted during their initial priming phase [13,14], but interestingly, the provision of IL-15 during vaccination is sufficient to rescue the secondary cytotoxic T lymphocyte response in the absence of $CD4^+$ T cells, likely due to IL-15 mediated suppression of the proapoptotic molecule Bax and induction of the anti-apoptotic molecule Bcl-xl [28,37]. IL-15 production by antigen presenting DCs is necessary even in the presence of $CD4^+$ T cells to allow for the secondary responsiveness of $CD8^+$ T cells. These studies suggest a model in which DCs gain the ability to secrete IL-15 following $CD4^+$ T cell-mediated licensing.

IL-2 is also important during priming to imprint the secondary responsiveness of $CD8^+$ T cells [39,40]. $CD4^+$ T cells have been suggested as a critical source of IL-2, although other studies have found that $CD8^+$ T cells produce the IL-2 that is necessary for their own development. [26,27,41–43], with licensed DCs enabling such autocrine secretion. Autocrine IL-2 allows for the induction of NGFI-A binding protein 2 (Nab2) in $CD8^+$ T cells, which mediates suppression of TRAIL expression and allows for secondary expansion of these cells [43]. Licensed DCs also produce IL-12p70 that acts directly on antigen-specific $CD8^+$ T cells to increase their expression of CD25, rendering these cells more responsive to IL-2 [41,44].

Regulatory $CD4^+$ T (T_{REG}) cells can act to modulate IL-2 exposure of effector $CD8^+$ T cells during the priming phase and are necessary for the generation of functional memory $CD8^+$ T cells following immunization (Fig. 1b) [45–48]. For instance, competitive consumption of IL-2 by T_{REG} cells can limit the availability of IL-2 to early activated $CD8^+$ T cells, which suppressed $CD8^+$ T cell expansion, but enhanced the functional responsiveness of memory $CD8^+$ T cells following secondary challenge [45]. While autocrine IL-2 expression is necessary for the generation of functional memory $CD8^+$ T cells, prolonged exposure to IL-2 early after immunization promotes their terminal differentiation [49,50]. T_{REG} cells also modulate the maturation state of DCs through leukocyte-associated antigen 1 (LFA-1) and cytotoxic T lymophocyte-associated antigen 4 (CTLA4)-mediated regulation of CD80/86 expression, which may influence the ability of DCs to stimulate $CD8^+$ T cells during priming [51,52]. T_{REG} cells in addition regulate the stability of interactions between DCs and $CD8^+$ T cells through suppression of chemokine production by DCs, and are critical for the development of high-avidity effector and memory $CD8^+$ T cells [53–57]. Additional mechanisms by which T_{REG} cells can regulate memory formation following infection are discussed in the following section.

$CD4^+$ T cell help following systemic infection

Despite it being appreciated that $CD4^+$ T cells are necessary for $CD8^+$ T cell memory maturation following acute pathogen infection, the mechanism(s) by which this help is mediated, and which CD4 T cells are involved is still being understood [14,19,58–61]. One study showed that $CD4^+$ T cells are required after the priming and expansion phase (i.e., during the contraction phase) and that this help can be antigen non-specific[60]. $CD4^+$ T cell help following LCMV infection is independent of CD40-mediated licensing of DCs or $CD8^+$ T cells, with passive transfer of LCMV-specific antibodies sufficient to restore a protective memory $CD8^+$ T cell response in the absence of CD40-CD40L interactions through the

facilitation of viral clearance [62,63]. "Helpless" CD8$^+$ T cells displayed increased expression of T-bet, a transcription factor involved in fine-tuning CD8$^+$ effector and memory T cell differentiation, with reduction of T-bet expression restoring the functionality of these cells [64,65]. Additionally, CD4$^+$ T cell help influences the epigenetic state of memory CD8$^+$ T cells with "helpless" CD8$^+$ T cells displaying reduced acetylation at the IFNγ locus and increased methylation at the IL-2 promoter resulting in reduced responsiveness upon restimulation [66]. Interestingly, treatment with a histone deacetylase inhibitor is sufficient to restore the responsiveness of "helpless" CD8$^+$ T cells [67].

Effector CD4$^+$ T cells induced following pathogen infection display considerable phenotypic and functional heterogeneity that can influence their ability to provide help (Box 1). Insight into the specific mechanism(s) underlying CD4$^+$ T cell help was provided by the finding that IL-10, which is normally thought of as an immunosuppressive cytokine, is important for memory CD8$^+$ T cell development. Although normal numbers of memory CD8 T cells form in the absence of IL-10, the maturation of these cells was impaired, particularly the development of T_{CM} cells [68–70]. The cellular source of IL-10 needed to promote the phenotypic and functional qualities of the memory CD8$^+$ T cells was unclear from these studies. Multiple cell types including myeloid cells, DCs, and T cells can secrete IL-10 following LCMV infection [71,72]. Interestingly, and somewhat counterintuitively, we found that T_{REG} cells act as the relevant source of IL-10 required for memory CD8$^+$ T cell maturation following LCMV infection. In line with the kinetics of CD4 T cell help identified earlier [60], T_{reg} cell-derived IL-10 primarily acted during the resolution phase to promote memory maturation through suppression of proinflammatory cytokine production by DCs (Fig. 2a, b) [47]. Conceptually similar, a separate study found that T_{REG} cells influence CD8$^+$ T cell memory maturation through CTLA-4 mediated suppression of effector and proliferation programs in effector CD8$^+$ T cells [48]. Thus, T_{REG} cells through multiple mechanisms can promote functional memory CD8$^+$ T cell development.

Box 1

Effector CD4$^+$ T cell differentiation

Following antigen recognition, naïve CD4$^+$ T cell can differentiate into distinct effector T helper cell lineages capable of differentially regulating the immune response. The inflammatory environment in which recently activated CD4$^+$ T cells develop in drives their polarization and allows T cells to match their effector function to the pathogen encountered. Viral infection induces high levels of pro-inflammatory cytokines such as IL-12, IFNγ, and type I IFNs that promote the induction of Th1 cells. Conversely, IL-4 produced following helminth infection or allergic responses drives Th2 cell differentiation, while fungal infection induces TGFβ and IL-6 secretion that promote Th17 cell differentiation [108]. T follicular helper (Tfh) cell differentiation is regulated by STAT3 signaling cytokines such as IL-6 and IL-21 and is dependent on iterative interactions with cognate DCs and B cells [111–115]. CD4$^+$ T cell subsets can be identified through 1) expression of cell surface markers such as Ly6C, PSGL1, CXCR5, and PD1; 2) expression of canonical transcriptions factors T-bet, Gata3, Rorγt, and Bcl6; and 3) secretion of cytokines such as IFNγ, TNFα, IL-4, IL-5, IL-13, IL-17, and IL-21.

Considerable plasticity exists among effector $CD4^+$ T cell subsets *in vivo* which helps facilitate the generation of a diverse immune response capable of mediating pathogen clearance, promoting the humoral response, and restraining immunopathology [108].

In addition to this function, T_{REG} cells can act during the priming phase to suppress the magnitude of the $CD8^+$ T cell response thereby restricting the number of cells that survive into the memory phase [73–75]. However, type I IFNs generated early after infection can directly inhibit T_{REG} cell activation and proliferation facilitating the generation of an optimal effector T cell response [76]. As type I IFNs wane, T_{reg} cell expansion occurs with the newly populating T_{REG} cells displaying an activated phenotype with more robust IL-10 expression relative to T_{REG} cells present at steady state (Box 2) [47,77]. IL-10-competent T_{REG} cells are primarily located in the white pulp of the spleen, near to DCs as well as memory precursor $CD8^+$ T cells, positioning them optimally to suppress the activation state of DCs thus insulating $CD8^+$ T cells from excess bystander inflammation and preserving their memory precursor-state [47,65,78–80].

Box 2

Regulatory $CD4^+$ T cell differentiation

Regulatory $CD4^+$ T (T_{REG}) cells express the transcription factor FoxP3 and are critical in the prevention of excess immunopathology or autoimmunity through multiple mechanisms[116]. T_{REG} cells possess considerable functional and phenotypic heterogeneity. Central or naïve T_{REG} cells express CD62L and are predominantly found in circulation and secondary lymphoid tissues. Following exposure to antigen and/or IL-2, T_{REG} cells adopt a more effector-like state and downregulate CD62L and progressively upregulate CD69 and KLRG1. Acquisition of a more effector like phenotype is accompanied by enhanced expression of suppressive molecules such as IL-10 and CTLA4 with $KLRG1^+$ T_{REG} cells representing a terminally differentiated population [47,77].

Effector T_{REG} cells appear to co-opt the transcriptional network of effector $CD4^+$ T cells in order to match their suppressive function to their present environment. T-bet^+ T_{REG} cells express the chemokine receptors CXCR3 and CCR4 and regulate skin and lung inflammation. STAT3-expressing T_{REG} cells upregulate CCR6 and regulate gut homeostasis, while Bcl6-expressing T_{REG} cells display high levels of CXCR5 and regulate the germinal center response. T_{REG} cells also accumulate in adipose tissue, with these cells distinguished by expression of PPARγ and are important in regulating adipose metabolism [117]. T_{REG} cells have recently been identified in the muscle where they are promote muscle repair through secretion of the growth factor amphiregulin [118].

$CD4^+$ T cell help following mucosal infection

$CD8^+$ T_{RM} cells are critical in guarding mucosal surfaces against pathogen challenge [81]. While $CD4^+$ T cells are not needed to initiate a primary virus-specific response following mucosal infection by pathogens such as influenza, they are necessary for the optimal

development of a memory $CD8^+$ T cell population capable of mediating protective immunity [18,75]. However, until recently the role of $CD4^+$ T cells in mediating tissue-specific $CD8^+$ T cell memory was unclear. Insight into this question was provided by work showing that $CD4^+$ T cell help is needed for entry into the female reproductive tract following mucosal viral infection [82]. $CD4^+$ T cells indirectly mediated the entry of $CD8^+$ T cells into the tissue through IFNγ-dependent induction of chemokines by locally infected cells (Fig. 3a) [82]. While $CD4^+$ T cells do not appear necessary for $CD8^+$ T cell entry into the skin following viral infection, $CD4^+$ skin T_{RM} cells can facilitate recruitment of circulating $CD8^+$ T cells into the skin in a CXCR3-dependent manner following challenge with *Leishmania major* [83,84].

We extended these studies to find that $CD4^+$ T cells are important for the development of airway-homing $CD8^+$ T_{RM} cells following influenza virus infection [85]. While $CD8^+$ T cells entered the lung in the absence of $CD4^+$ T cell help, they failed to properly localize to the lung airways and had a reduced ability to recruit $CD8^+$ T cells from circulation and mediate protective immunity upon heterosubtypic challenge. “Helpless” $CD8^+$ T cells also displayed enhanced expression of T-bet, which rendered these cells less responsive to TGFb-mediated induction of CD103, an integrin essential for T_{RM} cell maintenance in the tissue [85]. Together, these studies provided a model in which IFNγ-producing $CD4^+$ T cells directed effector $CD8^+$ T cell migration into particular areas of certain mucosal tissues that then facilitated their exposure to signals, such as TGFβ, necessary for their continued maturation into $CD103^+$ T_{RM} cells (Fig. 3b).

T_{REG} cells also may play a role in the formation of $CD8^+$ T_{RM} cells. In the absence of T_{REG} cells, reduced numbers of $CD8^+$ T_{RM} cells were retained in the central nervous system (CNS) following West Nile virus infection. The reduction in T_{RM} cell numbers is associated with decreased amounts of TGFβ in the CNS suggesting that T_{reg}-dependent modulation of TGFβ levels may be important in driving $CD8^+$ T_{RM} cell formation and retention in mucosal tissues (Fig. 3c)[86]. Together these findings highlight a new, perhaps ironic, role for T_{REG} cells in providing “helper” as opposed to suppressive functions for the generation of long-term T cell immunity.

$CD4^+$ T cell help following chronic infection

$CD4^+$ T cells play critical roles in the long-term maintenance of $CD8^+$ T cell responses in multiple models of chronic viral infection [87–91]. A central component of $CD4^+$ T cell help in this setting is the secretion of IL-21 [92,93]. IL-21 sensing by $CD8^+$ T cells is necessary for the avoidance of clonal deletion and maintenance of effector activity even in the presence of $CD4^+$ T cells [94]. IL-21-production by $CD4^+$ T cells in individuals infected with the human immunodeficiency virus type 1 (HIV-1) correlates with $CD8^+$ T cell functionality and viral control, suggesting that this pathway might be an important therapeutic target [95–97].

Persistence of high antigen levels is a key driver of $CD8^+$ T cell functional exhaustion during chronic viral infection [98]. Therefore, an additional indirect role of $CD4^+$ T cell-derived IL-21 in bolstering the $CD8^+$ T cell response during chronic infection may be through promoting viral control. Multiple effector $CD4^+$ T cell subsets are capable of secreting IL-21

following viral infection including follicular helper T (Tfh) and Th1 cells [99]. Viral persistence promotes the differentiation of Tfh cells, which are necessary for the maintenance of the germinal center (GC) response and the continued production of virus-specific antibodies in the face of prolonged high levels of virus replication and immunosuppression [100,101]. Tfh cell-derived IL-21 is also critical for the GC response with a deficiency in IL-21 resulting in impaired maintenance of the GC along with reduced affinity maturation and isotype class switching [102–104]. Together, these studies suggest that Tfh-cell derived IL-21 is needed to promote the virus-specific humoral response thus allowing for the continued control of viremia and the prevention of terminal exhaustion.

IL-2 treatment also can enhance $CD8^+$ T cell responses during chronic infection and allows for enhanced control of viral burden [40,105]. The beneficial effect of such treatment is limited in the absence of $CD4^+$ T cells, which can serve as a source of IL-2 during chronic infection [106]. IL-2 therapy also results in an increase in the number of T_{REG} cells [106]. T_{REG} cells adopt an activated phenotype during chronic viral infection and have enhanced expression of molecules related to their suppressive activity including CTLA4, CD39, and IL-10 [71,107]. Depletion of T_{REG} cells during chronic infection resulted in a marked expansion of functional $CD8^+$ T cells through a process dependent on $CD4^+$ T cells and the expression of costimulatory molecules on DCs [107]. T_{REG} depletion alone was not sufficient to reduce viral burden, but did lead to significant reduction in viral titers when combined with PD-L1 blockade [107]. Therefore, in contrast to acute infection, suppression of the maturation state of DCs by T_{REG} cells during chronic infection serves to dampen long-term effector CD8+ T cell responses.

Concluding remarks and perspective

A temporal model for the function of $CD4^+$ T cells in regulating $CD8^+$ T cell maturation into distinct subsets capable of mediating protective immunity following viral infection has begun to emerge (Fig. 4).

During the priming phase $CD4^+$ T cells, through IFNγ-mediated chemokine induction, license $CD8^+$ T cell entry into mucosal tissues and facilitate their migration into a tissue microenvironment where they can sense signals necessary for their long-term residence [82,85]. Effector $CD4^+$ T cells also help facilitate viral clearance through the induction of an anti-viral humoral response, as well as directly through the secretion of effector molecules and cytokines [108]. Rapid viral clearance is important in restricting the degree of exposure of $CD8^+$ T cells to antigen and inflammation thus preventing functional exhaustion. High levels of type I IFN present during this stage of infection also restrict T_{REG} cell expansion and allow for a robust effector T cell response [76].

During the resolution phase, as type I IFN levels wane, there is an expansion of activated T_{REG} cells. IL-10 secretion by activated T_{REG} cells can suppress the maturation state of DCs and limit their secretion of pro-inflammatory cytokines thus allowing for the preservation of less differentiated effector $CD8^+$ T cells [47]. T_{REG} cell expression of CTLA-4 acts in a similar manner by limiting CD80/86 stimulation on DCs by CD28 [48]. Effector $CD8^+$ T cells are then able to continue to mature and develop into memory $CD8^+$ T cells capable of

rapidly responding upon pathogen reencounter. T_{REG} cells also act during the resolution phase to modulate TGFβ levels within mucosal tissues thereby bolstering the induction of $CD8^+$ T_{RM} cells [86]. Following the resolution phase, $CD4^+$ T cells may contribute to the maintenance of memory $CD8^+$ T cells through suppression of the outgrowth of viral reservoirs that could drive terminal exhaustion of $CD8^+$ T cells.

This Review has focused on recent advances providing insight into the role of $CD4^+$ T cell help in promoting the maturation of memory $CD8^+$ T cell following immunization and infection. As our understanding of the mechanisms underlying $CD4^+$ T cell help grows it will be important to harness these findings therapeutically to bolster vaccine efficacy. Considering the difficulties surrounding previous attempts at developing effective T cell based vaccines it may be necessary to modify existing vaccination approaches to more closely mirror the natural response to infection. This may be particularly relevant for vaccines to mucosal viruses such as influenza and HIV to which it will likely be necessary to induce T_{CM}, T_{EM}, and T_{RM} populations in order to optimally protect the host. Work is underway to develop vaccines capable of driving $CD8^+$ T cells into mucosal sites and exposing them to the signals necessary for their continued maintenance in the tissue, similar to the function of $CD4^+$ T cells during mucosal infection [9,109]. Therapeutic interventions designed to suppress inflammatory levels in individuals following vaccination through expansion of T_{REG} cells or provision of IL-10 may also be a novel approach to bolstering systemic T cell immunity. Individuals suffering from chronic infection have impaired development of protective immunity following vaccination, potentially due to high levels of bystander inflammation, and would be an attractive target for this type of intervention [110]. Continued study of the mechanisms underlying $CD4^+$ T cell help should provide clearer understanding into how we can harness the utility of $CD4^+$ T cells to improve vaccine efficacy.

References

1. Ahmed R, Gray D. Immunological memory and protective immunity: understanding their relation. Science. 1996; 272:54–60. [PubMed: 8600537]
2. La Gruta NL, Turner SJ. T cell mediated immunity to influenza: mechanisms of viral control. Trends Immunol. 2014; 35:396–402. [PubMed: 25043801]
3. Korber BT, Letvin NL, Haynes BF. T-cell vaccine strategies for human immunodeficiency virus, the virus with a thousand faces. J Virol. 2009; 83:8300–8314. [PubMed: 19439471]
4. Kaech SM, Ahmed R. Memory CD8+ T cell differentiation: initial antigen encounter triggers a developmental program in naïve cells. Nat Immunol. 2001; 2:415–422. [PubMed: 11323695]
5. Kaech SM, Cui W. Transcriptional control of effector and memory CD8+ T cell differentiation. Nat Rev Immunol. 2012; 12:749–761. [PubMed: 23080391]
6. Stary G, et al. A mucosal vaccine against Chlamydia trachomatis generates two waves of protective memory T cells. Science. 2015; 348:aaa8205. [PubMed: 26089520]
7. Sathaliyawala T, et al. Distribution and compartmentalization of human circulating and tissue-resident memory T cell subsets. Immunity. 2013; 38:187–197. [PubMed: 23260195]
8. Schenkel JM, Fraser KA, Vezys V, Masopust D. Sensing and alarm function of resident memory $CD8^+$ T cells. Nat Immunol. 2013; 14:509–513. [PubMed: 23542740]
9. Shin H, Iwasaki A. A vaccine strategy that protects against genital herpes by establishing local memory T cells. Nature. 2012; 491:463–467. [PubMed: 23075848]

10. Wu T, et al. Lung-resident memory CD8 T cells (TRM) are indispensable for optimal cross-protection against pulmonary virus infection. J Leukoc Biol. 2014; 95:215–224. [PubMed: 24006506]
11. Schenkel JM, et al. T cell memory. Resident memory CD8 T cells trigger protective innate and adaptive immune responses. Science. 2014; 346:98–101. [PubMed: 25170049]
12. Ariotti S, et al. T cell memory. Skin-resident memory $CD8^+$ T cells trigger a state of tissue-wide pathogen alert. Science. 2014; 346:101–105. [PubMed: 25278612]
13. Janssen EM, et al. CD4+ T cells are required for secondary expansion and memory in CD8+ T lymphocytes. Nature. 2003; 421:852–856. [PubMed: 12594515]
14. Shedlock DJ, Shen H. Requirement for CD4 T cell help in generating functional CD8 T cell memory. Science. 2003; 300:337–339. [PubMed: 12690201]
15. Sun JC, Bevan MJ. Defective CD8 T cell memory following acute infection without CD4 T cell help. Science. 2003; 300:339–342. [PubMed: 12690202]
16. Bourgeois C, Rocha B, Tanchot C. A role for CD40 expression on CD8+ T cells in the generation of CD8+ T cell memory. Science. 2002; 297:2060–2063. [PubMed: 12242444]
17. Riberdy JM, Christensen JP, Branum K, Doherty PC. Diminished primary and secondary influenza virus-specific CD8(+) T-cell responses in CD4-depleted Ig(−/−) mice. J Virol. 2000; 74:9762–9765. [PubMed: 11000251]
18. Belz GT, Wodarz D, Diaz G, Nowak MA, Doherty PC. Compromised influenza virus-specific CD8(+)-T-cell memory in CD4(+)-T-cell-deficient mice. J Virol. 2002; 76:12388–12393. [PubMed: 12414983]
19. von Herrath MG, Yokoyama M, Dockter J, Oldstone MB, Whitton JL. CD4-deficient mice have reduced levels of memory cytotoxic T lymphocytes after immunization and show diminished resistance to subsequent virus challenge. J Virol. 1996; 70:1072–1079. [PubMed: 8551565]
20. Wiesel M, Oxenius A. From crucial to negligible: Functional CD8+T-cell responses and their dependence on CD4+T-cell help. Eur J Immunol. 2012; 42:1080–1088. [PubMed: 22539281]
21. Bennett SR, et al. Help for cytotoxic-T-cell responses is mediated by CD40 signalling. Nature. 1998; 393:478–480. [PubMed: 9624004]
22. Bennett SR, Carbone FR, Karamalis F, Miller JF, Heath WR. Induction of a CD8+ cytotoxic T lymphocyte response by cross-priming requires cognate CD4+ T cell help. J Exp Med. 1997; 186:65–70. [PubMed: 9206998]
23. Ridge JP, Di Rosa F, Matzinger P. A conditioned dendritic cell can be a temporal bridge between a CD4+ T-helper and a T-killer cell. Nature. 1998; 393:474–478. [PubMed: 9624003]
24. Schoenberger SP, Toes RE, van der Voort EI, Offringa R, Melief CJ. T-cell help for cytotoxic T lymphocytes is mediated by CD40-CD40L interactions. Nature. 1998; 393:480–483. [PubMed: 9624005]
25. Hervas-Stubbs S, Olivier A, Boisgerault F, Thieblemont N, Leclerc C. TLR3 ligand stimulates fully functional memory CD8+ T cells in the absence of CD4+ T-cell help. Blood. 2007; 109:5318–5326. [PubMed: 17339421]
26. Wilson EB, Livingstone AM. Cutting edge: CD4+ T cell-derived IL-2 is essential for help-dependent primary CD8+ T cell responses. The Journal of Immunology. 2008; 181:7445–7448. [PubMed: 19017930]
27. Sokke Umeshappa C, et al. CD154 and IL-2 signaling of CD4+ T cells play a critical role in multiple phases of CD8+ CTL responses following adenovirus vaccination. PLoS ONE. 2012; 7:e47004. [PubMed: 23071696]
28. Oh S, et al. IL-15 as a mediator of CD4+ help for CD8+ T cell longevity and avoidance of TRAIL-mediated apoptosis. Proc Natl Acad Sci USA. 2008; 105:5201–5206. [PubMed: 18362335]
29. Zloza A, et al. NKG2D signaling on $CD8^+$ T cells represses T-bet and rescues CD4-unhelped $CD8^+$ T cell memory recall but not effector responses. Nat Med. 2012; 18:422–428. [PubMed: 22366950]
30. Sacks JA, Bevan MJ. TRAIL deficiency does not rescue impaired CD8+ T cell memory generated in the absence of CD4+ T cell help. J Immunol. 2008; 180:4570–4576. [PubMed: 18354179]
31. Castellino F, et al. Chemokines enhance immunity by guiding naive CD8+ T cells to sites of CD4+ T cell-dendritic cell interaction. Nature. 2006; 440:890–895. [PubMed: 16612374]

32. Kumamoto Y, Mattei LM, Sellers S, Payne GW, Iwasaki A. CD4+ T cells support cytotoxic T lymphocyte priming by controlling lymph node input. Proc Natl Acad Sci USA. 2011; 108:8749–8754. [PubMed: 21555577]
33. Eickhoff S, et al. Robust Anti-viral Immunity Requires Multiple Distinct T Cell-Dendritic Cell Interactions. Cell. 2015; 162:1322–1337. [PubMed: 26296422]
34. Hor JL, et al. Spatiotemporally Distinct Interactions with Dendritic Cell Subsets Facilitates CD4(+) and CD8(+) T Cell Activation to Localized Viral Infection. Immunity. 201510.1016/j.immuni.2015.07.020
35. Castellino F, Germain RN. Chemokine-guided CD4+ T cell help enhances generation of IL-6RalphahighIL-7Ralpha high prememory CD8+ T cells. J Immunol. 2007; 178:778–787. [PubMed: 17202339]
36. Azadniv M, Bowers WJ, Topham DJ, Crispe IN. CD4+ T cell effects on CD8+ T cell location defined using bioluminescence. PLoS ONE. 2011; 6:e16222. [PubMed: 21283759]
37. Janssen EM, et al. CD4+ T-cell help controls CD8+ T-cell memory via TRAIL-mediated activation-induced cell death. Nature. 2005; 434:88–93. [PubMed: 15744305]
38. Hamilton SE, Wolkers MC, Schoenberger SP, Jameson SC. The generation of protective memory-like CD8+ T cells during homeostatic proliferation requires CD4+ T cells. Nat Immunol. 2006; 7:475–481. [PubMed: 16604076]
39. Williams MA, Tyznik AJ, Bevan MJ. Interleukin-2 signals during priming are required for secondary expansion of CD8+ memory T cells. Nature. 2006; 441:890–893. [PubMed: 16778891]
40. Bachmann MF, Wolint P, Walton S, Schwarz K, Oxenius A. Differential role of IL-2R signaling for CD8+ T cell responses in acute and chronic viral infections. Eur J Immunol. 2007; 37:1502–1512. [PubMed: 17492805]
41. Wiesel M, et al. Th cells act via two synergistic pathways to promote antiviral CD8+ T cell responses. The Journal of Immunology. 2010; 185:5188–5197. [PubMed: 20881183]
42. Feau S, Arens R, Togher S, Schoenberger SP. Autocrine IL-2 is required for secondary population expansion of CD8(+) memory T cells. Nat Immunol. 2011; 12:908–913. [PubMed: 21804558]
43. Wolkers MC, et al. Nab2 regulates secondary CD8+ T-cell responses through control of TRAIL expression. Blood. 2012; 119:798–804. [PubMed: 22128144]
44. Obar JJ, et al. CD4+ T cell regulation of CD25 expression controls development of short-lived effector CD8+ T cells in primary and secondary responses. Proc Natl Acad Sci USA. 2010; 107:193–198. [PubMed: 19966302]
45. de Goër de Herve MG, Jaafoura S, Vallée M, Taoufik Y. FoxP3^{+} regulatory CD4 T cells control the generation of functional CD8 memory. Nat Commun. 2012; 3:986. [PubMed: 22871805]
46. McNally A, Hill GR, Sparwasser T, Thomas R, Steptoe RJ. CD4+CD25+ regulatory T cells control CD8+ T-cell effector differentiation by modulating IL-2 homeostasis. Proc Natl Acad Sci USA. 2011; 108:7529–7534. [PubMed: 21502514]
47. Laidlaw BJ, et al. Production of IL-10 by CD4(+) regulatory T cells during the resolution of infection promotes the maturation of memory CD8(+) T cells. Nat Immunol. 2015; 16:871–879. [PubMed: 26147684]
48. Kalia V, Penny LA, Yuzefpolskiy Y, Baumann FM, Sarkar S. Quiescence of Memory CD8(+) T Cells Is Mediated by Regulatory T Cells through Inhibitory Receptor CTLA-4. Immunity. 2015; 42:1116–1129. [PubMed: 26084026]
49. Kalia V, et al. Prolonged interleukin-2Ralpha expression on virus-specific CD8+ T cells favors terminal-effector differentiation in vivo. Immunity. 2010; 32:91–103. [PubMed: 20096608]
50. Pipkin ME, et al. Interleukin-2 and inflammation induce distinct transcriptional programs that promote the differentiation of effector cytolytic T cells. Immunity. 2010; 32:79–90. [PubMed: 20096607]
51. Misra N, Bayry J, Lacroix-Desmazes S, Kazatchkine MD, Kaveri SV. Cutting edge: human CD4+CD25+ T cells restrain the maturation and antigen-presenting function of dendritic cells. J Immunol. 2004; 172:4676–4680. [PubMed: 15067041]
52. Onishi Y, Fehervari Z, Yamaguchi T, Sakaguchi S. Foxp3+ natural regulatory T cells preferentially form aggregates on dendritic cells in vitro and actively inhibit their maturation. Proc Natl Acad Sci USA. 2008; 105:10113–10118. [PubMed: 18635688]

53. Tang Q, et al. Visualizing regulatory T cell control of autoimmune responses in nonobese diabetic mice. Nat Immunol. 2006; 7:83–92. [PubMed: 16311599]
54. Tadokoro CE, et al. Regulatory T cells inhibit stable contacts between CD4+ T cells and dendritic cells in vivo. J Exp Med. 2006; 203:505–511. [PubMed: 16533880]
55. Morlacchi S, et al. Regulatory T cells target chemokine secretion by dendritic cells independently of their capacity to regulate T cell proliferation. The Journal of Immunology. 2011; 186:6807–6814. [PubMed: 21572026]
56. Dal Secco V, et al. Tunable chemokine production by antigen presenting dendritic cells in response to changes in regulatory T cell frequency in mouse reactive lymph nodes. PLoS ONE. 2009; 4:e7696. [PubMed: 19893746]
57. Pace L, et al. Regulatory T cells increase the avidity of primary CD8+ T cell responses and promote memory. Science. 2012; 338:532–536. [PubMed: 23112334]
58. Leist TP, Cobbold SP, Waldmann H, Aguet M, Zinkernagel RM. Functional analysis of T lymphocyte subsets in antiviral host defense. J Immunol. 1987; 138:2278–2281. [PubMed: 2435794]
59. Buller RM, Holmes KL, Hügin A, Frederickson TN, Morse HC. Induction of cytotoxic T-cell responses in vivo in the absence of CD4 helper cells. Nature. 1987; 328:77–79. [PubMed: 2955227]
60. Sun JC, Williams MA, Bevan MJ. CD4+ T cells are required for the maintenance, not programming, of memory CD8+ T cells after acute infection. Nat Immunol. 2004; 5:927–933. [PubMed: 15300249]
61. Novy P, Quigley M, Huang X, Yang Y. CD4 T cells are required for CD8 T cell survival during both primary and memory recall responses. J Immunol. 2007; 179:8243–8251. [PubMed: 18056368]
62. Sun JC, Bevan MJ. Cutting edge: long-lived CD8 memory and protective immunity in the absence of CD40 expression on CD8 T cells. J Immunol. 2004; 172:3385–3389. [PubMed: 15004136]
63. Bachmann MF, Hunziker L, Zinkernagel RM, Storni T, Kopf M. Maintenance of memory CTL responses by T helper cells and CD40-CD40 ligand: antibodies provide the key. Eur J Immunol. 2004; 34:317–326. [PubMed: 14768036]
64. Intlekofer AM, et al. Requirement for T-bet in the aberrant differentiation of unhelped memory CD8+ T cells. J Exp Med. 2007; 204:2015–2021. [PubMed: 17698591]
65. Joshi NS, et al. Inflammation directs memory precursor and short-lived effector CD8(+) T cell fates via the graded expression of T-bet transcription factor. Immunity. 2007; 27:281–295. [PubMed: 17723218]
66. Northrop JK, Thomas RM, Wells AD, Shen H. Epigenetic remodeling of the IL-2 and IFN-gamma loci in memory CD8 T cells is influenced by CD4 T cells. J Immunol. 2006; 177:1062–1069. [PubMed: 16818762]
67. Northrop JK, Wells AD, Shen H. Cutting edge: chromatin remodeling as a molecular basis for the enhanced functionality of memory CD8 T cells. The Journal of Immunology. 2008; 181:865–868. [PubMed: 18606637]
68. Brooks DG, Walsh KB, Elsaesser H, Oldstone MBA. IL-10 directly suppresses CD4 but not CD8 T cell effector and memory responses following acute viral infection. Proc Natl Acad Sci USA. 2010; 107:3018–3023. [PubMed: 20133700]
69. Cui W, Liu Y, Weinstein JS, Craft J, Kaech SM. An interleukin-21-interleukin-10-STAT3 pathway is critical for functional maturation of memory CD8+ T cells. Immunity. 2011; 35:792–805. [PubMed: 22118527]
70. Foulds KE, Rotte MJ, Seder RA. IL-10 is required for optimal CD8 T cell memory following Listeria monocytogenes infection. J Immunol. 2006; 177:2565–2574. [PubMed: 16888018]
71. Parish IA, et al. Chronic viral infection promotes sustained Th1-derived immunoregulatory IL-10 via BLIMP-1. J Clin Invest. 2014; 124:3455–3468. [PubMed: 25003188]
72. Brooks DG, et al. Interleukin-10 determines viral clearance or persistence in vivo. Nat Med. 2006; 12:1301–1309. [PubMed: 17041596]

73. Suvas S, Azkur AK, Kim BS, Kumaraguru U, Rouse BT. CD4+CD25+ regulatory T cells control the severity of viral immunoinflammatory lesions. J Immunol. 2004; 172:4123–4132. [PubMed: 15034024]
74. Kursar M, et al. Regulatory CD4+CD25+ T cells restrict memory CD8+ T cell responses. J Exp Med. 2002; 196:1585–1592. [PubMed: 12486101]
75. Ballesteros-Tato A, León B, Lund FE, Randall TD. CD4+ T helper cells use CD154-CD40 interactions to counteract T reg cell-mediated suppression of CD8+ T cell responses to influenza. Journal of Experimental Medicine. 2013; 210:1591–1601. [PubMed: 23835849]
76. Srivastava S, Koch MA, Pepper M, Campbell DJ. Type I interferons directly inhibit regulatory T cells to allow optimal antiviral T cell responses during acute LCMV infection. Journal of Experimental Medicine. 2014; 211:961–974. [PubMed: 24711580]
77. Cheng G, et al. IL-2 receptor signaling is essential for the development of Klrg1+ terminally differentiated T regulatory cells. The Journal of Immunology. 2012; 189:1780–1791. [PubMed: 22786769]
78. Steinman RM, Pack M, Inaba K. Dendritic cells in the T-cell areas of lymphoid organs. Immunol Rev. 1997; 156:25–37. [PubMed: 9176697]
79. Jung YW, Rutishauser RL, Joshi NS, Haberman AM, Kaech SM. Differential localization of effector and memory CD8 T cell subsets in lymphoid organs during acute viral infection. The Journal of Immunology. 2010; 185:5315–5325. [PubMed: 20921525]
80. Stelekati E, et al. Bystander chronic infection negatively impacts development of CD8(+) T cell memory. Immunity. 2014; 40:801–813. [PubMed: 24837104]
81. Schenkel JM, Masopust D. Tissue-resident memory T cells. Immunity. 2014; 41:886–897. [PubMed: 25526304]
82. Nakanishi Y, Lu B, Gerard C, Iwasaki A. CD8+ T lymphocyte mobilization to virus-infected tissue requires CD4+ T-cell help. Nature. 2009; 462:510–513. [PubMed: 19898495]
83. Jiang X, et al. Skin infection generates non-migratory memory CD8+ TRM cells providing global skin immunity. Nature. 2012; 483:227–231. [PubMed: 22388819]
84. Glennie ND, et al. Skin-resident memory CD4+ T cells enhance protection against Leishmania major infection. Journal of Experimental Medicine. 201510.1084/jem.20142101
85. Laidlaw BJ, et al. CD4+ T cell help guides formation of CD103+ lung-resident memory CD8+ T cells during influenza viral infection. Immunity. 2014; 41:633–645. [PubMed: 25308332]
86. Graham JB, Da Costa A, Lund JM. Regulatory T cells shape the resident memory T cell response to virus infection in the tissues. The Journal of Immunology. 2014; 192:683–690. [PubMed: 24337378]
87. Zajac AJ, et al. Viral immune evasion due to persistence of activated T cells without effector function. J Exp Med. 1998; 188:2205–2213. [PubMed: 9858507]
88. Snyder CM, et al. CD4+ T cell help has an epitope-dependent impact on CD8+ T cell memory inflation during murine cytomegalovirus infection. The Journal of Immunology. 2009; 183:3932–3941. [PubMed: 19692644]
89. Kemball CC, et al. The antiviral CD8+ T cell response is differentially dependent on CD4+ T cell help over the course of persistent infection. J Immunol. 2007; 179:1113–1121. [PubMed: 17617604]
90. Cardin RD, Brooks JW, Sarawar SR, Doherty PC. Progressive loss of CD8+ T cell-mediated control of a gamma-herpesvirus in the absence of CD4+ T cells. J Exp Med. 1996; 184:863–871. [PubMed: 9064346]
91. Hunziker L, Klenerman P, Zinkernagel RM, Ehl S. Exhaustion of cytotoxic T cells during adoptive immunotherapy of virus carrier mice can be prevented by B cells or CD4+ T cells. Eur J Immunol. 2002; 32:374–382. [PubMed: 11813156]
92. Yi JS, Du M, Zajac AJ. A vital role for interleukin-21 in the control of a chronic viral infection. Science. 2009; 324:1572–1576. [PubMed: 19443735]
93. Elsaesser H, Sauer K, Brooks DG. IL-21 is required to control chronic viral infection. Science. 2009; 324:1569–1572. [PubMed: 19423777]
94. Fröhlich A, et al. IL-21 receptor signaling is integral to the development of Th2 effector responses in vivo. Blood. 2007; 109:2023–2031. [PubMed: 17077330]

95. Chevalier MF, et al. HIV-1-specific interleukin-21+ CD4+ T cell responses contribute to durable viral control through the modulation of HIV-specific CD8+ T cell function. J Virol. 2011; 85:733–741. [PubMed: 21047960]

96. Williams LD, et al. Interleukin-21-producing HIV-1-specific CD8 T cells are preferentially seen in elite controllers. J Virol. 2011; 85:2316–2324. [PubMed: 21159862]

97. Aubert RD, et al. Antigen-specific CD4 T-cell help rescues exhausted CD8 T cells during chronic viral infection. Proc Natl Acad Sci USA. 2011; 108:21182–21187. [PubMed: 22160724]

98. Mueller SN, Ahmed R. High antigen levels are the cause of T cell exhaustion during chronic viral infection. Proc Natl Acad Sci USA. 2009; 106:8623–8628. [PubMed: 19433785]

99. Hale JS, et al. Distinct Memory CD4+ T Cells with Commitment to T Follicular Helper- and T Helper 1-Cell Lineages Are Generated after Acute Viral Infection. Immunity. 2013:1–13.10.1016/j.immuni.2013.02.020

100. Fahey LM, et al. Viral persistence redirects CD4 T cell differentiation toward T follicular helper cells. J Exp Med. 2011; 208:987–999. [PubMed: 21536743]

101. Harker JA, Lewis GM, Mack L, Zuniga EI. Late interleukin-6 escalates T follicular helper cell responses and controls a chronic viral infection. Science. 2011; 334:825–829. [PubMed: 21960530]

102. Linterman MA, et al. IL-21 acts directly on B cells to regulate Bcl-6 expression and germinal center responses. J Exp Med. 2010; 207:353–363. [PubMed: 20142429]

103. Zotos D, et al. IL-21 regulates germinal center B cell differentiation and proliferation through a B cell-intrinsic mechanism. J Exp Med. 2010; 207:365–378. [PubMed: 20142430]

104. Rasheed MAU, et al. Interleukin-21 is a critical cytokine for the generation of virus-specific long-lived plasma cells. J Virol. 2013; 87:7737–7746. [PubMed: 23637417]

105. Blattman JN, et al. Therapeutic use of IL-2 to enhance antiviral T-cell responses in vivo. Nat Med. 2003; 9:540–547. [PubMed: 12692546]

106. West EE, et al. PD-L1 blockade synergizes with IL-2 therapy in reinvigorating exhausted T cells. J Clin Invest. 2013; 123:2604–2615. [PubMed: 23676462]

107. Penaloza-Macmaster P, et al. Interplay between regulatory T cells and PD-1 in modulating T cell exhaustion and viral control during chronic LCMV infection. Journal of Experimental Medicine. 2014; 211:1905–1918. [PubMed: 25113973]

108. Swain SL, McKinstry KK, Strutt TM. Expanding roles for CD4+ T cells in immunity to viruses. Nat Rev Immunol. 2012; 12:136–148. [PubMed: 22266691]

109. Wakim LM, Smith J, Caminschi I, Lahoud MH, Villadangos JA. Antibody-targeted vaccination to lung dendritic cells generates tissue-resident memory CD8 T cells that are highly protective against influenza virus infection. Mucosal Immunol. 201510.1038/mi.2014.133

110. Stelekati E, Wherry EJ. Chronic bystander infections and immunity to unrelated antigens. Cell Host Microbe. 2012; 12:458–469. [PubMed: 23084915]

111. Ma CS, et al. Functional STAT3 deficiency compromises the generation of human T follicular helper cells. Blood. 201210.1182/blood-2011-11-392985

112. Ray JP, et al. Transcription factor STAT3 and type I interferons are corepressive insulators for differentiation of follicular helper and T helper 1 cells. Immunity. 2014; 40:367–377. [PubMed: 24631156]

113. Eto D, et al. IL-21 and IL-6 are critical for different aspects of B cell immunity and redundantly induce optimal follicular helper CD4 T cell (Tfh) differentiation. PLoS ONE. 2011; 6:e17739. [PubMed: 21423809]

114. Choi YS, et al. ICOS receptor instructs T follicular helper cell versus effector cell differentiation via induction of the transcriptional repressor Bcl6. Immunity. 2011; 34:932–946. [PubMed: 21636296]

115. Shulman Z, et al. Dynamic signaling by T follicular helper cells during germinal center B cell selection. Science. 2014; 345:1058–1062. [PubMed: 25170154]

116. Vignali DAA, Collison LW, Workman CJ. How regulatory T cells work. Nat Rev Immunol. 2008; 8:523–532. [PubMed: 18566595]

117. Liston A, Gray DHD. Homeostatic control of regulatory T cell diversity. Nat Rev Immunol. 2014; 14:154–165. [PubMed: 24481337]

118. Burzyn D, et al. A special population of regulatory T cells potentiates muscle repair. Cell. 2013; 155:1282–1295. [PubMed: 24315098]

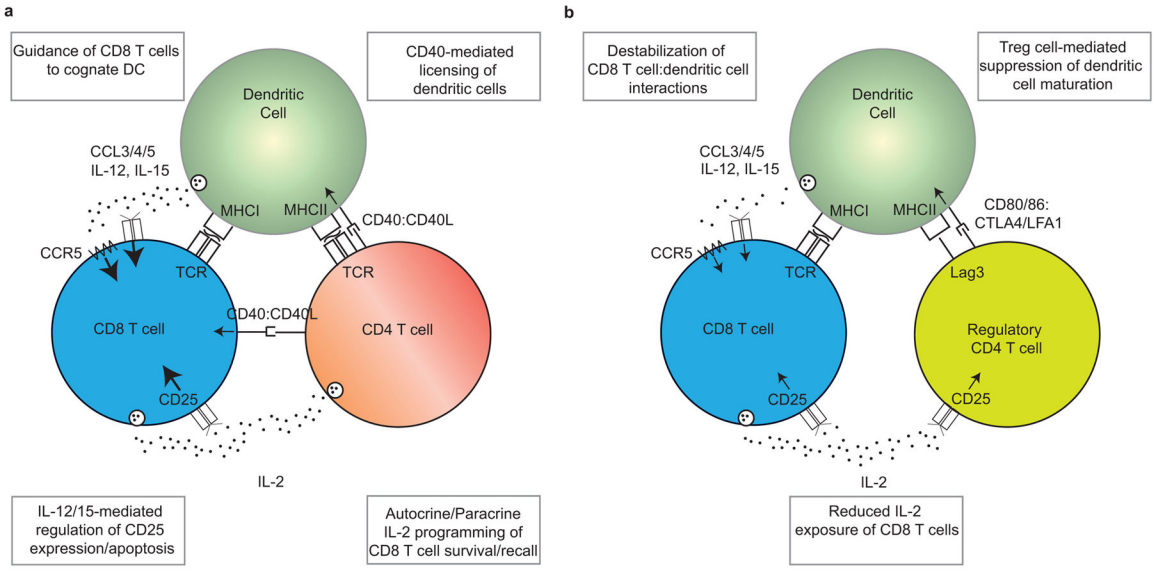

Figure 1. CD4$^+$ T cell help to CD8$^+$ T cells during immunization

a. Following immunization, naïve CD4$^+$ T cells interact with and license cognate dendritic cells (DCs) through a CD40-dependent process. Licensed DCs express higher levels of MHC and costimulatory molecules and can recruit naïve CD8$^+$ T to their cognate DC through secretion of the chemokines CCL3, 4, and 5. Licensed DCs also secrete IL-12 and IL-15, which increase expression of IL-2R (CD25) on CD8$^+$ T cells and promote cell survival, respectively. Enhanced expression of CD25 facilitates the responsive of CD8$^+$ T cells to IL-2 and promotes CD8$^+$ T cell survival and their ability to proliferate upon secondary antigen encounter. Both CD4$^+$ and CD8$^+$ T cells act as sources of the IL-2, with CD4$^+$ and CD8$^+$ T cells in some settings also directly interacting through CD40:CD40L. **b**. Regulatory T (T_{REG}) cells can modulate the CD8$^+$ T cell response following immunization by suppressing the maturation state of DCs, thereby limiting their ability to stimulate CD8$^+$ T cells. By limiting chemokine secretion by DCs, T_{REG} cells can destabilize CD8$^+$ T cell: DC interactions and accordingly promote the induction of high affinity effector and memory CD8$^+$ T cells. T_{REG} cells also limit the sensing of IL-2 by CD8$^+$ T cells by competing for available IL-2 and limiting the expression of CD25 by CD8$^+$ T cells through control of DC secretion of IL-12.

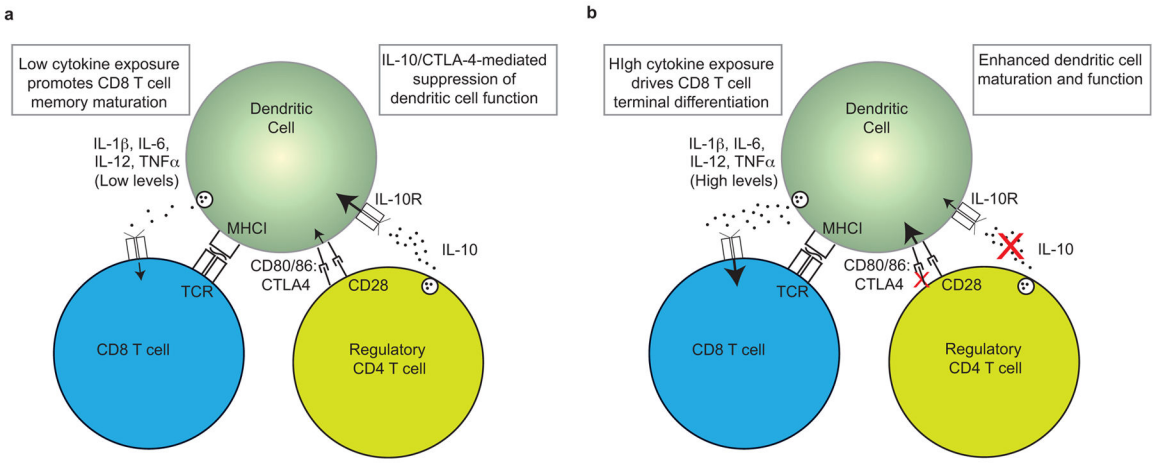

Figure 2. T_{REG} cells promote memory $CD8^+$ T cell maturation during viral infection

a. Following acute viral infection, T_{REG} cells expansion is initially suppressed due to the presence of high levels of type I IFNs. As type I IFNs wane, T_{REG} cell numbers increase with these cells adopting a more effector like phenotype marked by increased expression of IL-10 and CTLA-4. During the resolution phase of infection, T_{REG} cell-derived IL-10 acts to suppress the maturation state of DCs and limit their production of proinflammatory cytokines. T_{REG} cell expression of CTLA-4 acts in a similar manner through modulation of the CD28-CD80/86 signaling axis. Low levels of proinflammatory signals allow for the continued maturation of effector $CD8^+$ T cells into functional memory $CD8^+$ T cells. **b.** In the absence of T_{REG} cell-derived IL-10 and/or CTLA-4, DCs adopt a more mature phenotype and secrete higher levels of proinflammatory cytokines. The enhanced levels of proinflammatory cytokines are sensed by effector $CD8^+$ T cells and drive these cells to adopt a more terminally differentiated phenotype, limiting their ability to proliferate and mediate protective immunity upon reencounter with the pathogen.

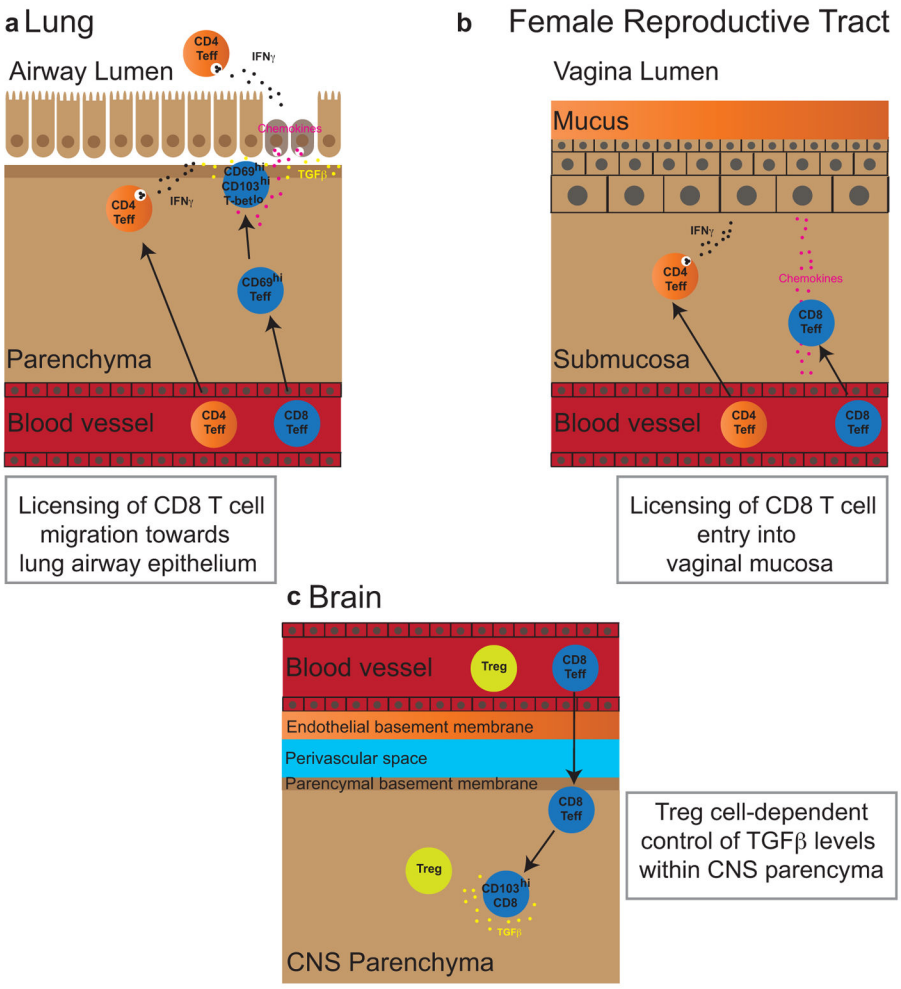

Figure 3. CD4$^+$ T cell help to CD8$^+$ T cell during mucosal infection

a. Following influenza virus infection, CD4$^+$ T cells rapidly migrate from the draining lymph node (dLN) to the lung airways where they mediate the release of chemokines from epithelial cells via secretion of IFNγ. As CD8$^+$ T cells move from the dLN to the lung parenchyma they upregulate CD69, likely due to exposure to inflammatory cytokines and T cell receptor signaling. These cells can then migrate towards the chemokine gradient surrounding the airway where they encounter TGFβ, which subsequently induces the expression of CD103 and suppression of the transcription factor T-bet, thereby promoting the establishment of a lung T_{RM} cell population. **b.** Following herpes simplex virus infection, CD4$^+$ T cells migrate from the draining lymph node (dLN) to the female reproductive tract (FRT) where they mediate the release of chemokines from the infected tissue via secretion of IFNγ. CD4$^+$ T cell-derived IFNγ is necessary for CD8$^+$ T cells to migrate into the virally infected FRT. **c.** Following West Nile virus infection, CD8$^+$ T cells primed in the dLN migrate to the central nervous system (CNS) parenchyma. T_{REG} cells also traffic to the CNS where they modulate the levels of TGFβ. T_{REG} cell-dependent control of TGFβ may modulate the expression of CD103 expression on CD8$^+$ T cells and accordingly influence their ability to reside long-term in the brain.

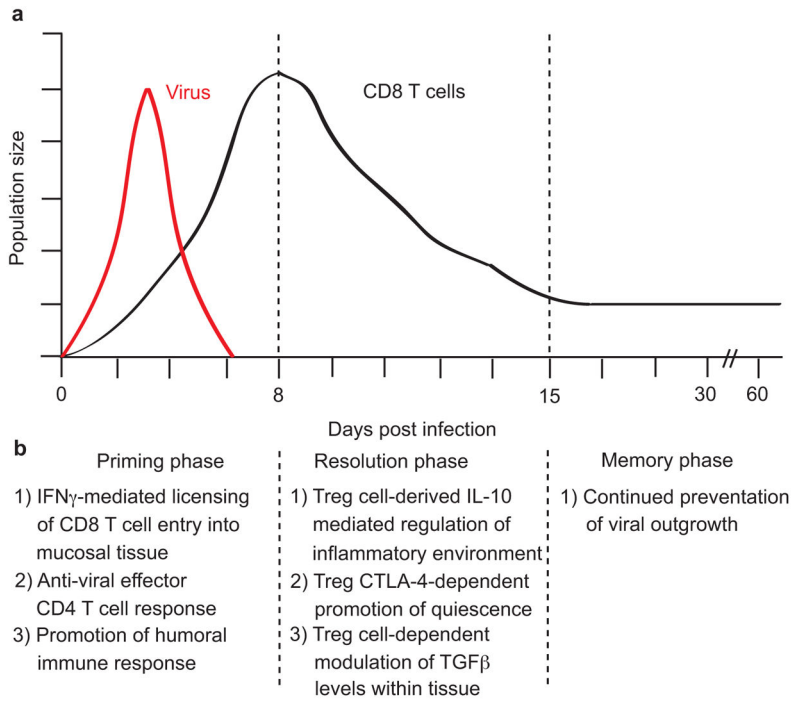

Figure 4. Temporal model of CD4$^+$ T cell help during viral infection

a. Following infection, antigen-specific T cells rapidly proliferate during priming and differentiate into cytotoxic T lymphocytes (CTLs) that mediate viral clearance. Most of these cells die over the next several weeks during the resolution phase of the response. Only a small percentage of effector T cells (5–10%) survive and further develop into functional mature memory CD8$^+$ T cells. **b.** CD4$^+$ T cells play distinct roles during these phases to regulate the development of CD8$^+$ T cell memory. During the priming phase, CD4$^+$ T cells license the entry of CD8$^+$ T cell into mucosal tissues and promote viral clearance through the induction of a virus-specific effector CD4$^+$ T cell and humoral response. Later in the resolution phase, T_{REG} cell-derived IL-10 facilitates the maturation of a mature memory CD8$^+$ T cell population and can promote functional quiescence of memory cell through expression of the inhibitory receptor CTLA-4. T_{REG} cells may also modulate TGFβ levels in mucosal sites to promote CD103 expression and accordingly regulate T_{RM} cell development. During the memory phase, the CD4$^+$ T cell-dependent immune response allows for continued suppression of viral outgrowth.