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Cytokines and T-cell homeostasis

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Homeostasis of T cells can be defined as the ability of the immune system to maintain normal T-cell counts and to restore T-cell numbers following T-cell depletion or expansion. These processes are governed by extrinsic signals, most notably cytokines. Two members of the common γ chain family of cytokines, interleukin (IL)-7 and IL-15, are central to homeostatic proliferation and survival of mature $CD4^+$ and $CD8^+$ T cells. Recent evidence suggests that other cytokines, including IL-2, IL-10, IL-12, interferons and TGF-β, as well as the transcription factors T-bet and eomesodermin all play important but different roles at distinct stages of T-cell homeostasis.

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Introduction

Throughout life, lymphocytes are maintained at fairly stable numbers by various homeostatic mechanisms. For mature post-thymic T cells, these mechanisms are mainly governed by cytokines. Thus, naïve T cells constantly receive low-level signals through contact with interleukin (IL)-7 and major histocompatibility complex (MHC) molecules. These signals do not induce proliferation but instead allow the cells to survive for prolonged periods in a quiescent state [1–5]. By contrast, memory T cells appear to maintain their numbers independently of contact with peptide–MHC complexes but are heavily dependent on signals received by cytokines. For $CD8^+$ memory cells, both IL-15 and IL-7 are important for homeostatic background proliferation and survival, whereas $CD4^+$ memory cells rely mainly on IL-7 (Figures 1 and 2). Memory cells include cells that result from immunization with defined antigens as well as naturally occurring 'memory-phenotype' cells; these latter cells share many phenotypic and functional characteristics of antigen-specific memory cells and are probably generated in response to environmental or self antigens [1,5].

In this article, we will review new insights into T-cell homeostasis from the recent literature, focusing on the past two years. We will attempt to integrate this new information into a framework in which multiple cytokines are central to homeostatic proliferation and survival of mature T cells.

$CD8^+$ T cells

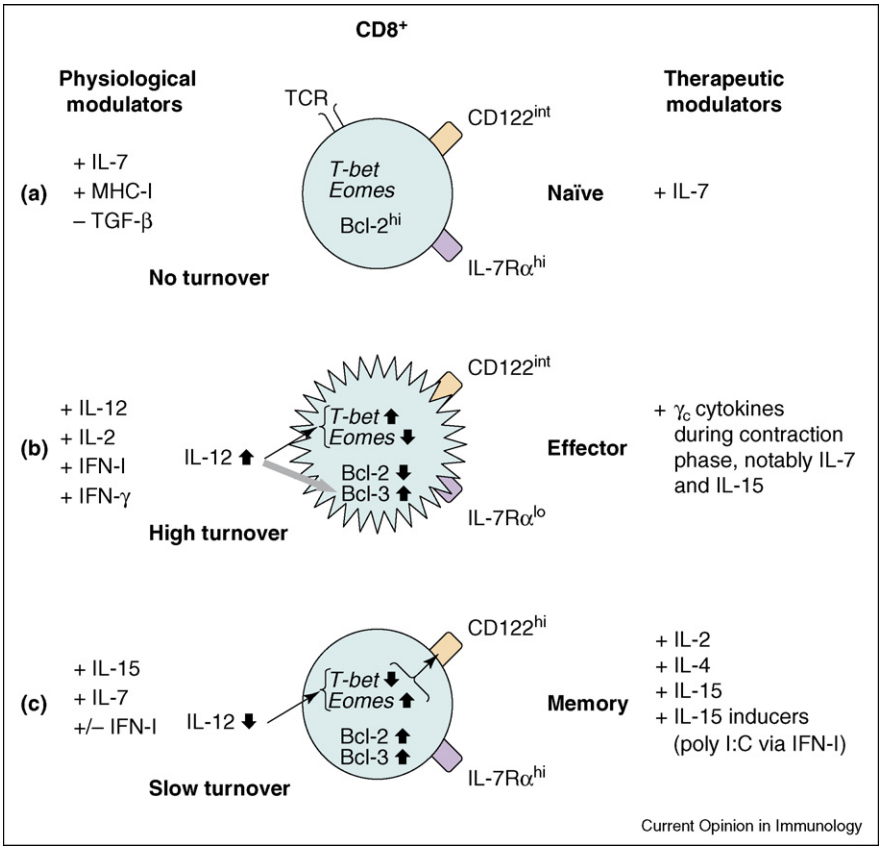
Common γ chain cytokines

IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 share the common γ chain (γ_c) cytokine receptor and are crucial for lymphocyte generation, survival and homeostasis. Two members of this group, namely IL-7 and IL-15, play a key role in $CD8^+$ T-cell homeostasis (Figure 1), as mentioned above. More recently, other γ_c cytokines, most notably IL-2, have been shown to regulate homeostasis of memory $CD8^+$ cells under defined conditions. Thus, after IL-2 injection, enhanced IL-2 signals augment proliferation and accumulation of $CD8^+$ memory cells, especially cells that express high levels of the IL-2/IL-15 receptor β chain (CD122). For these cells, signaling by IL-2 *in vivo* is considerably enhanced following association with certain anti-IL-2 monoclonal antibodies (mAbs) [6••,7,8]. Pronounced proliferation and accumulation of $CD8^+$ memory cells can also follow injection of IL-4 [6••] or reflect stimulation of IL-4 synthesis by natural killer (NK) T cells [9].

Recently, contact with IL-2 signals during primary infection was shown to endow virus-specific memory $CD8^+$ cells with the capacity to mount robust responses upon secondary antigen encounter [10•]. Moreover, *in vitro* studies showed that IL-2 was needed by $CD8^+$ cells for optimal expansion and survival at low cell densities, for efficient interferon (IFN)-γ production, and for regulation of their cytotoxic function through expression of the effector molecules perforin and granzymes [11–14].

As mentioned above, IL-7 plays a central role in the homeostasis of naïve and memory $CD8^+$ cells, implying competition for limiting amounts of IL-7. Based mainly on *in vitro* data, it has been suggested that transcriptional suppression and subsequent downregulation of the IL-7 receptor α chain (IL-7Rα) by a cell that is receiving signals from IL-7 (or IL-2, IL-4, IL-6 and IL-15) provides a mechanism whereby the greatest possible number of T cells can benefit from available resources of IL-7 and other prosurvival cytokines [15]. The physiological

Figure 1



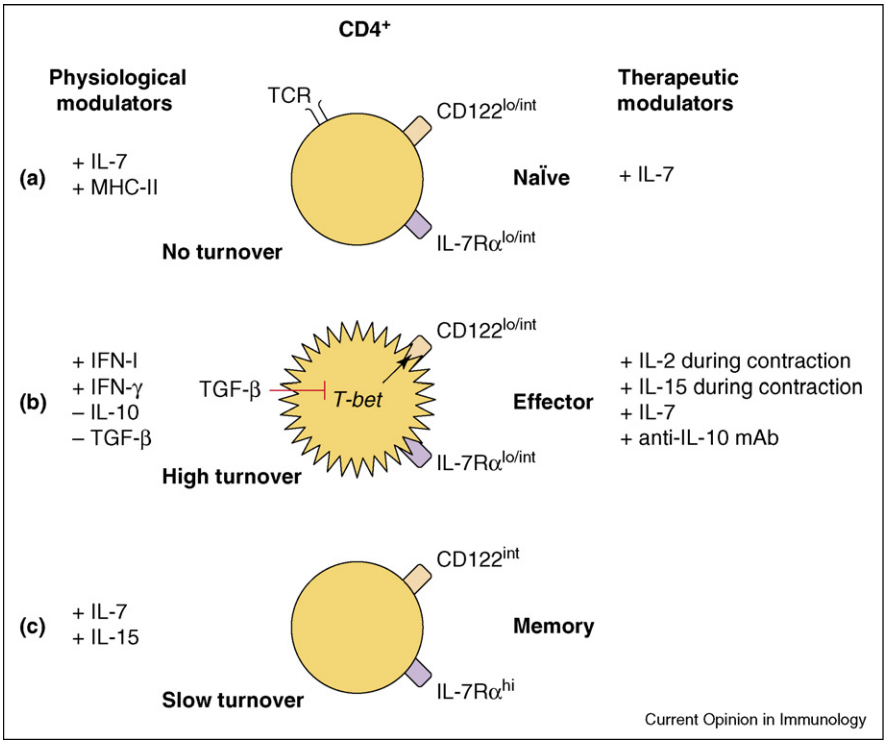
Cytokines that modulate CD8+ T-cell homeostasis. **(a)** Naïve CD8+ cells depend primarily on low-level signals through contact with IL-7 and major histocompatibility complex class I molecules (MHC-I), which allow them to survive for extended periods with little or no proliferation. This survival is mediated through sustaining high (hi) levels of the anti-apoptotic protein Bcl-2. Naïve CD8+ cells also receive inhibitory signals by way of TGF-β. **(b)** When naïve CD8+ cells become activated by antigen (signal 1) plus costimulation (signal 2) they require a third signal through IL-12 or IFN-I for efficient expansion, effector functions and subsequent memory formation. High IL-12 production during this phase leads to upregulation of T-bet and downregulation of eomesodermin (Eomes), and also to upregulation of the anti-apoptotic protein Bcl-3, whereas Bcl-2 and IL-7Rα levels decrease upon TCR engagement. Following vigorous expansion, the majority of the effector T cells die by apoptosis during the contraction phase, leaving a small fraction (~5–10%) of long-lived memory CD8+ cells. **(c)** Memory cells proliferate slowly in response to IL-15 and IL-7; this is facilitated through their expression levels of IL-2/15Rβ (CD122) and of IL-7Rα. IL-12 levels and, hence, T-bet and Eomes expression return to normal again; these latter two transcription factors in turn are responsible for maintaining high CD122 levels on CD8+ memory cells. For CD8+ memory cells, TGF-β inhibits proliferation whereas IFN-I can promote cell death in high concentrations but, via IL-15 production, might be stimulatory in low concentrations. Typical memory CD8+ cells that have a CD122hi phenotype are MHC-I-independent, but a subset of CD122lo memory CD8+ cells is MHC-I-dependent. The positive (+) and negative (–) influences mediated by cytokines under resting conditions or during an immune response are listed in the left column. Conversely, the right column shows ways to positively (+) modulate the respective CD8+ T-cell subset. For cytokines, their activity can be enhanced through association with anti-cytokine mAbs or, for IL-15, by binding to soluble recombinant IL-15Rα. Abbreviations: hi, high; int, intermediate; lo, low.

relevance of this model has been challenged recently by findings showing that *in vivo* regulation of IL-7Rα expression can occur independently of IL-7 [16] and can involve contact with IL-12 [17].

Given the central role of IL-7 and IL-15 in CD8+ T cell homeostasis, there is considerable interest in exploring their potential use as adjuvants in vaccines. Thus, administration of recombinant human IL-7 (rhIL-7) or rhIL-15 during immunization led to increased expansion of antigen-specific CD8+ cells; this was accompanied, however, by enhanced death of these cells during the contraction phase [18]. Nevertheless, the net effect of rhIL-7 or rhIL-15 administration was a long-term increase in the antigen-specific CD8+ memory pool. These data were recently confirmed by another group using the lymphocytic choriomeningitis virus (LCMV) system of infection [19].

The best-described role of IL-15 in CD8+ T-cell homeostasis is its contribution to homeostatic turnover and survival of memory cells [1], which involves the bone marrow as well as spleen and lymph nodes [20,21]. A recent report using IL-15-transgenic mice showed that

Figure 2



Cytokines that modulate CD4+ T-cell homeostasis. **(a)** Naïve CD4+ cells rely on signals through contact with IL-7 and major histocompatibility complex class II (MHC-II) molecules; such low-level stimulation does not induce proliferation but permits the cells to survive for extended periods. At this stage, CD4+ cells receive inhibitory TGF-β signals. **(b)** When naïve CD4+ cells become activated by antigen they downregulate IL-7Rα and undergo vigorous proliferation. This expansion is positively controlled by IFN-I and IFN-γ and is negatively influenced by the presence of IL-10 or administration of IL-2. As for CD8+ cells, most (~90–95%) of the effector CD4+ cells subsequently disappear during the following contraction phase, giving rise to small numbers of long-lived memory CD4+ cells. **(c)** Memory cells depend on IL-7 and, to a lesser extent, on IL-15 for slow turnover and survival, which reflects their int/hi expression levels of CD122 and IL-7Rα; most although not all of these cells are MHC-II-independent. At the memory CD4+ stage, TGF-β plays a negative role in inhibiting T-bet-induced expression of CD122. The positive (+) and negative (–) influences mediated by cytokines under resting conditions or during an immune response are listed in the left column. The right column lists ways to modulate positively (+) the respective CD4+ T-cell subset. Abbreviations: hi, high; int, intermediate; lo, low.

antigen-specific CD8+ cells underwent less cell death during the contraction phase when exposed to the increased IL-15 levels [22]. This is somewhat contrary to the data mentioned above, whereby administration of rhIL-15 led to increased apoptosis during the contraction phase [18]. In addition to acting by itself, IL-15 also cooperates with another γ_c cytokine — IL-21. Thus, a combination of IL-15 and IL-21 *in vitro* induced potent proliferation and IFN-γ production by naïve and memory CD8+ cells [23]. The physiological relevance of such a synergy is suggested by the finding that *ex vivo* and *in vivo* responses of CD8+ T cells, including antigen-specific expansion and cytotoxicity, were decreased in IL-21R$^{-/-}$ mice; conversely, administration of IL-15 together with IL-21 synergistically increased CD8+ cell-mediated anti-tumor activity [23]. IL-15 can also enhance the survival of memory CD8+ cells by controlling upregulation of 4-1BB, which has been shown to influence secondary CD8+ cell responses to viruses [24].

In terms of cytokine signaling pathways, suppressor of cytokine signaling-1 (SOCS-1) is crucial for regulating responsiveness of naïve CD8+ cells to IL-15 signals and T-cell receptor (TCR) triggering by self-ligands [25•,26]. Thus, SOCS-1$^{-/-}$ naïve CD8+ cells adoptively transferred to normal (T-cell sufficient) hosts showed considerably increased background proliferation, and this hyperresponsiveness was abrogated in the absence of either IL-15 or MHC class I [25•]. Notably, SOCS-1$^{-/-}$ mice contained above-normal numbers of memory-phenotype CD8+ cells but, unlike normal resting CD122^{hi} memory CD8+ cells, SOCS-1$^{-/-}$ memory-phenotype CD8+ cells might continue to receive TCR signals *in vivo*. Similarly, the subset of CD122^{lo} memory-phenotype CD8+ cells present in normal mice was recently shown to be largely dependent on contact with MHC class I molecules, but not γ_c cytokines, for their homeostasis [27]. For normal memory CD8+ cells, recent evidence has shown that the two highly homologous T-box transcription factors T-bet and eomesodermin are crucial for maintaining high levels of CD122

on these cells. Thus, combined removal of T-bet and eomesodermin led to downregulation of CD122 on memory $CD8^+$ cells (and NK cells) and to the disappearance of these IL-15-dependent cells [28••], which mimics the situation as seen in IL-$15^{-/-}$ mice [1].

Interleukin-12 and interferon

Mescher *et al.* [29•] have proposed that, in addition to receiving signals by antigen and costimulatory receptors, naïve $CD8^+$ T cells require a 'third' signal by IL-12 or type I IFN (IFN-I; comprising IFN-α and -β) for optimal proliferation and effector functions. The molecular events that control this third signal are not clear to date, but recent evidence suggested that, whereas antigen and costimulatory signals were sufficient for upregulation of the anti-apoptotic proteins Bcl-2 and Bcl-x_L, IL-12 was needed for Bcl-3 upregulation [30,31]. $CD8^+$ T cells primed *in vitro* in the presence of IL-12 were shown to confer better *in vivo* protection against virus challenge [32]. However, $CD8^+$ cells primed directly under *in vivo* conditions that lack IL-12 failed to show any defect in primary or memory T-cell responses [32], implying a certain redundancy for IL-12, perhaps by IFN-α [29]. In fact, IFN-α has been shown to act directly on $CD8^+$ cells to improve expansion of antigen-specific $CD8^+$ cells *in vivo* [33,34]. This direct stimulatory effect of IFN-I on antigen-specific $CD8^+$ cells was most evident upon LCMV infection [35]. However, IFN-I might also have negative roles following acute viral infection by promoting apoptosis of memory $CD8^+$ cells [36]. In addition to IFN-I, IFN-γ can stimulate $CD8^+$ T cells to mediate increased expansion during viral infection [37]. As well as their direct effects, IFN-I and IFN-γ have a potent indirect influence on memory $CD8^+$ cell homeostasis as they can induce production of IL-15 and IL-15Rα in antigen-presenting cells (APCs) (Figure 3).

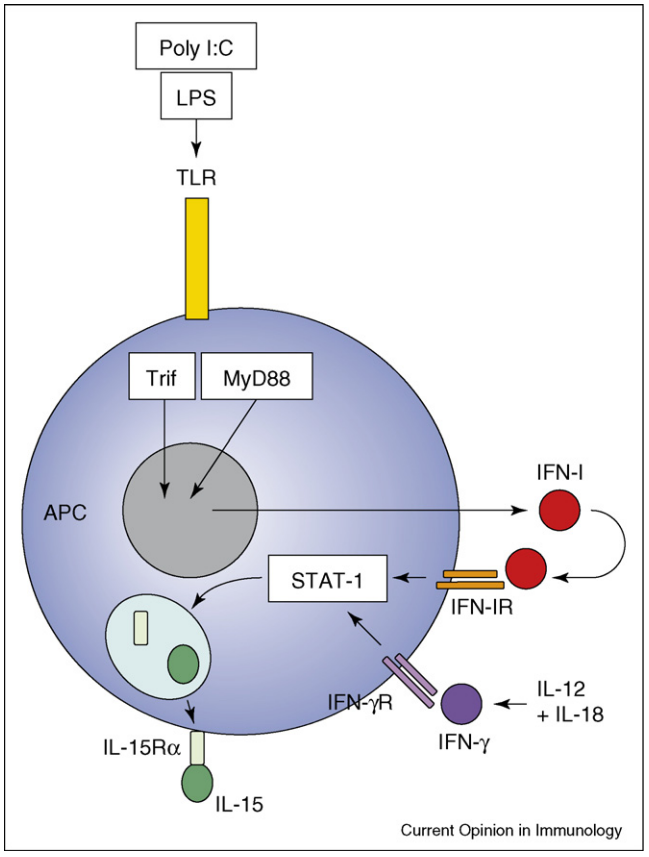
Like IFN-I, IL-12 can act directly on $CD8^+$ cells and is reported to be involved in the regulation of T-bet and eomesodermin (see above). Thus, IL-12 production during the effector phase of an immune response leads to increased T-bet and decreased eomesodermin expression; conversely, memory $CD8^+$ cells show lower T-bet and higher eomesodermin levels, reflecting an absence of IL-12 signaling in these cells [17].

Inhibitory cytokines: transforming growth factor-β and interleukin-10

Transforming growth factor-β (TGF-β) is known to have important inhibitory functions in the immune system, but its direct role in $CD8^+$ T-cell homeostasis is less clear. This was investigated recently in mice that had a T cell targeted deletion of a crucial subunit of the TGF-β receptor (TGF-βRII). Such mice displayed defects in thymic $CD8^+$ T-cell development, and mature $CD8^+$ T cells showed markers of activated cells ($CD44^{hi}$, $CD62L^{lo}$) and a 5–6 times faster rate of background proliferation than that in normal mice [38•]. This implies chronic stimulation, perhaps by self antigens.

IL-10, another immunoregulatory cytokine, can affect $CD8^+$ T-cell homeostasis. Thus, the presence of IL-10 during acute infection led to higher frequency and protective capacity of antigen-specific effector and memory $CD8^+$ cells [39], although $CD8^+$ T cells primed in the presence of IL-10 showed reduced secondary responses [40]. A different role of IL-10 has been observed during chronic infections. The anergic phenotype of $CD8^+$ T cells found in chronic LCMV infections was caused by

Figure 3



Signals that lead to IL-15 production. Several cell types including antigen-presenting cells (APCs) produce and present IL-15 to T cells and NK cells. Signals by pathogen-associated molecular patterns (such as Poly I:C and lipopolysaccharide [LPS]) trigger specific Toll-like receptors (TLRs), which are expressed in high levels on APCs. Once activated, TLRs signal through the adaptor molecules Trif and MyD88, and induce production of inflammatory cytokines including IFN-I. IFN-I acts in an autocrine and paracrine fashion on APCs to activate the production of IL-15 and IL-15Rα in a STAT-1-dependent fashion. IL-15 and its receptor subunit assemble in intracellular compartments and are brought to the cell surface where they are presented *in trans* to CD122/γ_c-bearing cells, most notably $CD8^+$ memory, NK and $CD4^+$ memory cells. An alternative pathway leading to IL-15/IL-15Rα production and presentation is mediated through IL-12- and IL-18-induced IFN-γ secretion, which activates STAT-1 as well.

IL-10 production, mainly by APCs; genetic removal or blocking of IL-10 signals led to functional recovery of $CD8^+$ T cells *in vivo* and to clearance of chronic LCMV infection [41••,42].

$CD4^+$ T cells

Common γ chain cytokines

Although IL-2 was originally described as a T-cell growth factor, the role of IL-2 had to be revised when IL-$2^{-/-}$ mice were found to contain above normal T-cell numbers and develop severe autoimmunity. Currently, the best-defined role of IL-2 for $CD4^+$ cells is in the maintenance of tolerance by supporting survival of $CD4^+CD25^+$ regulatory T cells (Tregs) [43]. For naïve $CD4^+$ cells, chimera studies showed that IL-2Rα$^{-/-}$ $CD4^+$ T cells generated normal numbers of effector and memory cells in the presence of Tregs [10•], indicating that IL-2 is not required during the primary immune response. However, IL-2 can clearly boost immune responses in certain situations (Figure 2), and in humans the ability of virus-specific $CD4^+$ cell numbers to synthesize IL-2 is one of the hallmarks of a successful anti-HIV T-cell response [44,45].

The result of therapeutic IL-2 administration appears to be crucially dependent upon the timing of treatment. Thus, IL-2 administration during the priming and effector phases of acute virus infection in mice had a negative effect on numbers of effector and memory $CD4^+$ cells [46]. By contrast, IL-2 treatment during the contraction phase dramatically reduced death of antigen-specific $CD4^+$ cells, which led to increased numbers of $CD4^+$ memory cells for up to half a year. A similar long-lasting boost in $CD4^+$ memory cells was also observed following administration of IL-2 or IL-15 to rhesus macaques during the contraction phase of the $CD4^+$ cell response following influenza infection [47]. These results are in line with evidence that homeostasis of memory $CD4^+$ cells is partly dependent on IL-15, and that IL-15 treatment causes the proliferation of memory $CD4^+$ cells *in vivo* [48–50].

$CD4^+$ memory cells decline slowly but progressively following acute virus infection and depend on IL-7 for their survival (reviewed in [51]). IL-7 also enhances the survival of $CD4^+$ effector cells, but is required continuously for their persistence [19]. As naïve, effector and memory $CD4^+$ cells all require IL-7 for their survival, this raises the crucial question of how these different populations are maintained in the face of competition from each other for limiting levels of IL-7. One study reports that $CD4^+$ memory cells have the advantage as they can prevent the homeostatic, or IL-7-driven, expansion of naïve $CD4^+$ cells in lymphopenic mice [52]. Interestingly, the presence of memory $CD4^+$ cells did not prevent the creation of a naïve $CD4^+$ cell pool, suggesting the presence of mechanisms that ensure the survival of all $CD4^+$ cells.

Interferons, interleukin-10 and transforming growth factor-β

Although IFNs have been the subject of much research, little is known about the direct effect of IFN-I on $CD4^+$ cells. As was observed for $CD8^+$ cells, a recent study using IFN-IR$^{-/-}$ $CD4^+$ cells demonstrated that IFN-I acts directly on $CD4^+$ cells to generate normal numbers of effector cells in response to viral infection [53]. Evidence that IFN-I signals prevented the death of $CD4^+$ effector cells was found in mice that lacked IFN regulatory factor 4 (IRF4) [54]. Thus, IRF4$^{-/-}$ $CD4^+$ cells were found to be highly sensitive to TCR-induced apoptosis, both *in vivo* and *in vitro*, although the mechanism of this cell death is unclear as it was Fas-independent and $CD4^+$ cells had normal levels of pro-apoptotic molecules. Similar to IFN-I, little is known about the direct effect of IFN-γ on $CD4^+$ cells, although it was demonstrated that IFN-γ signals can boost the size of a $CD4^+$ T-cell immune response [55].

As discussed above for $CD8^+$ cells, a recent study showed that IL-10 is expressed early by APCs during chronic virus infection, and that selective depletion of this cytokine could largely restore the function of antigen-specific $CD4^+$ cells in this setting [41••].

TGF-β is known to have a suppressive influence on multiple cell types. Notably, TGF-β inhibited T-bet-induced expression of CD122 on $CD4^+$ cells, thereby presumably limiting the response of these cells to IL-15 and IL-2 [38•]. Nevertheless, TGF-β can also have a stimulatory effect and is required for the survival of Tregs as well as $CD4^+$ effector cells [38•].

Conclusions

It is now becoming increasingly clear that T-cell homeostasis is influenced by multiple cytokines, which provides novel opportunities for selectively increasing the proportions of certain subsets or decreasing others. In the case of $CD8^+$ cells, these cells can be expanded *in vivo* by injection of IL-2, IL-4 or IL-15, especially when complexed with specific mAbs [6••,7,8] or, for IL-15, with soluble IL-15Rα [49,50] (Figures 1 and 2).

The influence of other cytokines such as IFNs, IL-12, TGF-β and IL-10 on T cells is highly complex and we are only beginning to understand the interplay between these cytokines and various transcription factors, which in turn regulate responsiveness of cells to other cytokines. One such example is the role of IL-12 in regulating levels of T-bet and eomesodermin, which influence responsiveness of memory $CD8^+$ cells to IL-15 through regulation of CD122 expression levels. Further efforts in this direction might provide useful tools for manipulating the level of the transcription factors involved in T-cell homeostasis.

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