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# Homeostasis of memory T cells

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Acknowledgements
This work was supported by NIH grants CA038355, AI046710, AG001743, AI045809, AG020186. O. Boyman was supported by fellowships from the Swiss National Science Foundation & Novartis Foundation. J. F. Purton was supported by fellowship from Australian NHMRC. Publication number 18042-IMM from The Scripps Research Institute.

*Immunological Reviews 2006*
*Vol. 211: 154–163*

Immunological Reviews
0105-2896

**Summary:** The pool of memory T cells is regulated by homeostatic mechanisms to persist for prolonged periods at a relatively steady overall size. Recent work has shown that two members of the common γ chain (γc) family of cytokines, interleukin-7 (IL-7) and IL-15, govern homeostasis of memory T cells. These two cytokines work in conjunction to support memory T-cell survival and intermittent background proliferation. Normal animals contain significant numbers of spontaneously arising memory-phenotype (MP) cells, though whether these cells are representative of true antigen-specific memory T cells is unclear. Nevertheless, it appears that the two types of memory cells do not display identical homeostatic requirements. For antigen-specific memory $CD8^+$ T cells, IL-7 is primarily important for survival while IL-15 is crucial for their background proliferation. For memory $CD4^+$ T cells, IL-7 has an important role, whereas the influence of IL-15 is still unclear.

## Introduction

Memory T cells typically arise at the end of an immune response and are formed from a small fraction of activated naïve T cells that have undergone massive expansion and differentiation into effector cells (1, 2). Memory T cells are long-lived and provide long-term protection against the pathogen concerned. The longevity of memory T cells was once thought to be mediated by signals arising from contact with sequestered antigens but is now known to be maintained by members of the common γ chain (γc) family of cytokines, namely interleukin-7 (IL-7) and IL-15. Before discussing homeostasis of memory T cells, it is helpful to briefly review the signals necessary for the generation and maintenance of the naïve T-cell pool.

## Homeostasis of naïve T cells

Naïve T cells are produced in the thymus from bone marrow (BM)-derived precursors, which, upon successful rearrangement of their T-cell receptor (TCR), undergo massive IL-7-driven expansion and differentiation into immature CD4 and CD8 double positive (DP) thymocytes (3–5). DP cells are subjected to positive and negative selection for expression of appropriate TCR that have low but significant reactivity for

self-peptide/major histocompatibility complex (MHC) ligands expressed on epithelial cells and BM-derived cells. Only a tiny fraction of DP cells meets this requirement, and these cells survive to differentiate into mature T cells and exit to the periphery. Hence, T cells with covert affinity to self-peptide/MHC ligands are produced to form the naïve T-cell pool.

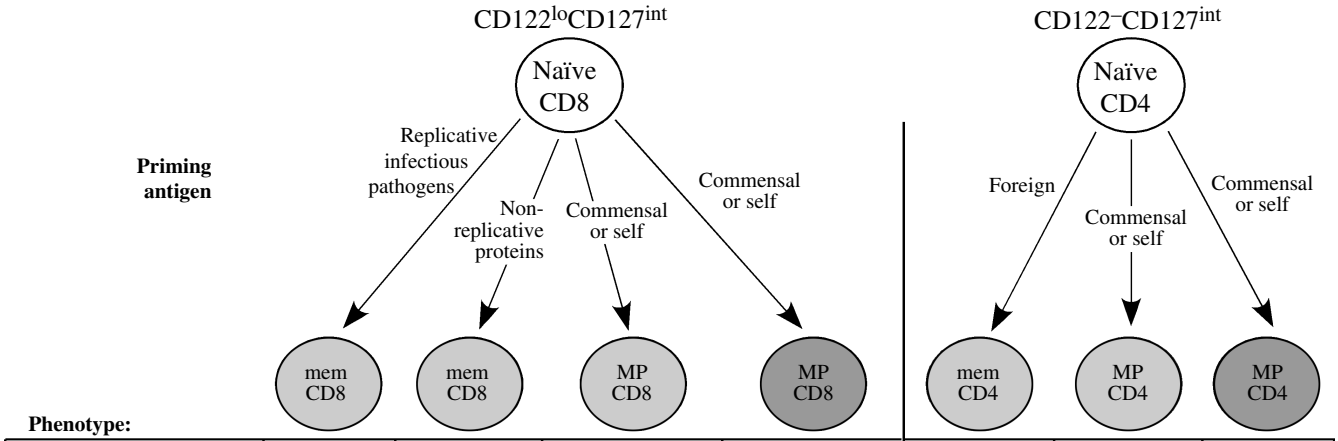
Most naïve T cells have a long lifespan, and until recently, such longevity was considered to be an inherent trait of these T cells (6–8). However, it is now well established, as with other cell types in the body, that the viability of naïve T cells is dependent on exogenous signals. In particular, long-term survival of naïve T cells requires a combination of signals arising from joint contact with self-peptide/MHC ligands and the cytokine IL-7 (9–14). Thus, when signaling from either of these self-components is abrogated, naïve T cells have an abbreviated lifespan of around 2–4 weeks. In contrast, overexpression of IL-7 leads to expansion of the naïve T-cell pool. IL-7 thus appears to be the primary cytokine for maintaining survival of naïve T cells, and the basal level of IL-7 appears to determine the overall size of the naïve T-cell pool.

IL-7 is a member of the relatively low molecular weight (15–20 kDa) family of cytokines, which includes IL-2, IL-4, IL-9, IL-15, and IL-21, whose receptors share a γc (15, 16). These cytokines affect lymphocytes at multiple stages of development, but their primary function appears to be to support cell survival and proliferation. Despite having overlapping functions, individual γc cytokines have specificity for particular cell populations. Such specificity is largely determined by the expression of specific cytokine receptors. Thus, for the T-cell lineage, IL-7 receptors (IL-7Rs) are expressed on early double negative thymic precursors, on mature naïve T cells, and then on memory T cells. However, IL-7Rs are not expressed at the DP cell stage or on recently activated mature T cells. As dictated by the expression pattern of its receptor, IL-7 is a nonredundant cytokine, being essential for T-cell proliferation and survival. Nevertheless, there are some overlapping functions for several γc cytokines, especially for IL-2, IL-7, and IL-15. For instance, IL-15 appears to play a partial role in supporting survival of naïve $CD8^+$ but not $CD4^+$ T cells. The tropism of IL-15 for naïve $CD8^+$ but not $CD4^+$ T cells correlates with the fact that $CD8^+$ T cells express low but significant levels of CD122 (IL-2Rβ), whereas naïve $CD4^+$ T cells lack these receptors.

### Origin of memory T cells (*Fig. 1*)

Memory T cells are known to arise from a small subset of effector cells that are generated from naïve T cells responding to foreign antigens (1, 2). Nonetheless, even in the absence of intentional immunization, T cells with the phenotype and characteristics of memory cells are present in low but significant numbers in early life and gradually expand with time to become the major population in old age (2, 17). Such spontaneously generated memory-phenotype (MP) cells are generally thought to be generated in response to various foreign antigens in the environment. However, some MP cells may arise purely through homeostatic mechanisms. Thus, it is now well established that naïve T cells can undergo homeostatic proliferation in response to self-peptide/MHC ligands in the presence of elevated levels of IL-7, as in lymphopenic conditions (18–21). The proliferating cells acquire characteristics of memory T cells, including the expression of characteristic cell surface markers and the ability to synthesize effector cytokines (22, 23). Significantly, MP cells are also present in germ-free mice raised in a completely sterile environment, even when fed a low molecular weight diet, thus preventing exposure to food antigens (24, 25). Hence, MP cells can arise without contact with foreign antigens.

In mice raised under conventional conditions, it is not possible to determine whether the bulk of MP T cells are generated in response to contact with foreign or self-antigens. For memory cells elicited by foreign antigens, there seems to be a hierarchy in terms of strength of stimulation. For instance, foreign antigens from a pathogenic viral infection, which are rapidly cleared, are likely to elicit strong but brief activation of naïve T cells, whereas non-replicative protein vaccines will induce weak stimulation. Similarly for MP cells, some of these cells are presumably generated in response to typical infectious agents, but others could be induced by antigens from non-pathogenic commensal bacteria that coexist indefinitely with the host; these antigens are likely to induce weaker but chronic activation of T cells. In addition, one can envisage that some MP cells could arise in response to self-antigens, including ubiquitous self-antigens; these ligands are likely to induce the weakest form of stimulation, even in the presence of elevated levels of homeostatic cytokines. The issue of the strength of the initial T-cell stimulus maybe relevant in considering the homeostatic requirements for memory T-cell populations. Thus, while homeostatic requirements for antigen-specific memory and MP T cells are similar, they apparently are not identical. Although direct data on this issue are sparse, such differences could reflect the variability in the initial conditions of activation, in particular the strength and duration of stimulation that initiates the differentiation of naïve T cells into memory T cells.




| Phenotype: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cytokine receptors | $CD122^{hi}$ $CD127^{hi}$ | $CD122^{hi}$ $CD127^{hi}$ | $CD122^{hi}$ $CD127^{hi}$ | $CD122^{lo}$ $CD127^{variable}$ | $CD122^{lo}$ $CD127^{hi}$ | $CD122^{lo}$ $CD127^{hi}$ | $CD122^{lo}$ $CD127^{hi}$ |
| Default state | resting | resting | resting | activated | resting | resting | activated |
| Background rate of homeostatic proliferation | Moderate | Moderate | Moderate/fast | Moderate/fast | Low | Low | Fast |
| Ag exposure | Acute | Acute | Acute? | Chronic? | Acute | Acute? | Chronic? |
| **Requirements for:** | | | | | | | |
| Survival | IL-7 | IL-15/ high IL-7 | IL-15/ high IL-7 | MHC-I | IL-7 | IL-7 | MHC-II |
| Homeostatic proliferation | IL-15 | IL-15 | IL-15 | MHC-I | IL-7/IL-15 | IL-7/IL-15 | MHC-II |

***Fig. 1.* Heterogeneity of memory T cells.** Memory (mem) and memory-phenotype (MP) T cells can be generated in response to foreign, commensal, or self-antigens. Foreign antigens can originate from replicative infectious pathogens or non-replicative protein antigens; these antigens will induce a strong immune response but are rapidly cleared. Commensal antigens refer to antigens from food or intestinal commensal bacteria; these and self-antigens are likely to elicit weak stimulation but are constantly available for chronic stimulation of T cells. The basic characteristics of memory T cells, including their phenotype, activation state, and homeostatic requirements, appear to be heavily influenced by the nature of the inducing antigen.

## Homeostasis of memory cells

The notion that memory cells are regulated by homeostatic mechanisms is indicated by the fact that the overall size of the memory T-cell pool in adults remains relatively constant over extended periods of time. In mice, the stability of total numbers of memory T cells applies even after multiple immunizations, suggesting that the influx of newly generated memory T cells is accommodated by reciprocal death of pre-existing memory T cells (26). Although regulation of the overall pool size applies to both naïve and memory T cells, distinct mechanisms appear to control homeostasis of these two cell types. This is apparent from their different rates of background turnover. Thus, whereas most naïve cells survive for many weeks or months in interphase, memory cells persist under normal conditions by undergoing intermittent cell division about once every 2 weeks (27).

In the 1990s, memory T cells were thought to be maintained by intermittent stimulation from TCR contact with trace amounts of sequestered foreign antigens or cross-reactive environmental antigens (28, 29). These possibilities now seem highly unlikely, as memory cells have been shown to survive not only in the absence of antigen but also in the absence of MHC molecules (10, 30–36). Hence, survival of memory cells appears to be completely independent of signaling through the TCR, either from contact with foreign or self-peptides. Nonetheless, foreign antigens may play an indirect role, for example, through activation of the innate immune system, thereby leading to production of key homeostatic cytokines required by memory cells. Homeostasis of memory $CD8^+$ and $CD4^+$ T cells is summarized below.

## Homeostasis of memory $CD8^+$ T cells

The realization that homeostasis of memory cells is independent of contact with MHC molecules focused attention on cytokines, some of which are known to support survival of memory cells under *in vitro* conditions. The initial clue that cytokines may be relevant under *in vivo* conditions came from the finding that activation of the innate immune system by a viral infection or injection of poly I:C or lipopolysaccharide (LPS) induced a temporary surge in the turnover rate of

memory $CD8^+$ T cells (37, 38). This finding applied to both antigen-specific and non-specific cells, suggesting that stimulation through the TCR was not essential and that soluble mediators are presumably involved in inducing TCR-independent 'bystander' proliferation of memory cells (37, 38). These and other findings showed that microbes and adjuvants induced bystander proliferation of memory $CD8^+$ T cells through the production of interferons (IFNs), especially type I IFNs (IFN-I) (37, 38). However, since IFN-I are strongly anti-proliferative, it seemed likely that IFN-I promoted proliferation through intermediary cytokine(s) that acted selectively on memory $CD8^+$ T cells. Here, it was notable that memory $CD8^+$ T cells expressed high levels of CD122 (IL-2Rβ), a receptor subunit for IL-2 and IL-15. It was subsequently found that IFN-I are powerful inducers of IL-15 synthesis (39, 40) and that bystander proliferation fails to occur in IL-$15^-$ hosts (41). IL-15 is now known to bridge the innate and adaptive immune systems and is produced by a wide variety of cell types (40, 42). Collectively, these findings have led to the current paradigm that stimulation of the innate immune system induces IFN-I synthesis, which in turn elicit production of IL-15. The latter binds directly to CD122 and mediates proliferation of memory $CD8^+$ T cells.

The receptor for IL-15 is comprised of three chains, α, β, and γ: the α chain is private for IL-15, whereas the β (CD122) and γ (CD132) chains are shared with the receptor for IL-2 (16). CD122 is expressed at the highest level on the majority (approximately 70%) of MP $CD8^+$ T cells in normal mice and at low but significant levels on naïve $CD8^+$ and MP $CD4^+$ cells; virtually no CD122 is expressed on naïve $CD4^+$ T cells (39). Reflecting the expression pattern of CD122, IL-15 proved to be essential for the turnover and survival of $CD122^{hi}$ MP $CD8^+$ T cells. Thus, the generation of IL-$15^-$ mice revealed that these mice lacked $CD122^{hi}$ MP $CD8^+$ T cells (41, 43). The absence of $CD122^{hi}$ MP $CD8^+$ T cells appeared to reflect a lack of cell survival rather than a developmental defect, as $CD122^{hi}$ MP $CD8^+$ T cells adoptively transferred into IL-$15^-$ mice failed to proliferate and disappeared rapidly (41). It should be mentioned that natural killer (NK) cells, which are $CD122^{hi}$, were also found to be exquisitely dependent on IL-15 for survival. Thus, like $CD122^{hi}$ MP $CD8^+$ T cells, NK cells are markedly reduced in IL-$15^-$ mice (43). IL-$15^-$ mice also show a 50% reduction in numbers of naïve $CD8^+$ cells, indicating that IL-15 plays a significant role in sustaining survival of naïve $CD8^+$ T cells (43, 44). Unlike $CD8^+$ T cells, the homeostasis of naïve and MP $CD4^+$ T cells is not noticeably affected in IL-$15^-$ mice (43).

The direct role of IL-15 on memory $CD8^+$ T cells is also indicated by the finding that overexpression of IL-15, as in IL-15 transgenic mice, increases the total numbers of $CD122^{hi}$ MP $CD8^+$ T cells (45, 46). As with other cytokines that signal through γc receptors, IL-15 probably supports survival of memory $CD8^+$ T cells by upregulating anti-apoptotic molecules such as Bcl-2. The signaling pathways triggered by IL-15 appear to be transmitted through signal transducer and activator of transcription 5 (STAT5) and are negatively modulated by suppressor of cytokine signaling-1 (SOCS-1). Thus, increased numbers of MP $CD8^+$ T cells are present in transgenic mice expressing a constitutively activated form of STAT5 (47) and, even more strikingly, in mice where the negative effect of SOCS-1 is abrogated, as in IFNγ$^-$SOCS-$1^-$ mice (48). In both cases, naïve $CD8^+$ T cells seem to display increased sensitivity to IL-15, which causes these cells to undergo spontaneous proliferation and subsequent differentiation into MP cells, this transition being dependent on TCR signaling from contact with self-peptide/MHC ligands (48, 49).

Despite considered as a soluble cytokine, IL-15 under *in vivo* conditions is presented in a cell-associated form bound to the IL-15Rα chain. The essential role of IL-15Rα for presentation of IL-15 was first observed with human cell lines (50). Subsequent work in mice showed that both IL-15 and IL-15Rα need to be synthesized by the same cell, indicating that IL-15 is preassociated with the IL-15Rα chain in the cytoplasm before expression on the cell surface (51). This unique mode of presentation explains the paradox that MP $CD8^+$ T cells transferred to IL-15$R\alpha^-$ mice fail to undergo bystander proliferation in response to poly I:C (52). This model also explains why IL-15$R\alpha^-$ mice lack MP $CD8^+$ T cells and confirms the authors' original suggestion that IL-15Rα is required for recognition of IL-15 (53). It should be noted that the IL-15Rα chain is expressed on many cell types, including T cells and antigen-presenting cells (APCs), and is readily upregulated upon activation of these cells, although only non-T cells appear to synthesize IL-15 (39, 54). Although the obligatory role for IL-15Rα expression on APC for presentation of IL-15 is clear, the reason why $CD8^+$ T cells express IL-15Rα is obscure. Thus, T-cell expression of IL-15Rα is largely dispensable for recognition of IL-15 by $CD8^+$ T cells, and expression of only the β and γ chains of IL-15R on $CD8^+$ T cells is sufficient for normal responses of memory $CD8^+$ T cells to IL-15 (52, 55). The function of IL-15Rα on $CD8^+$ T cells remains a mystery, but it could be involved in *trans*-presentation of soluble IL-15 to other T cells (50) or possibly for augmenting the activation of APCs (56).

Under normal conditions, the basal level of IL-15 is probably established by the constitutive production of IL-15 by DCs, which synthesize both IL-15 and IL-15Rα (51). Since production of IL-15 is efficiently induced by IFNs, especially by IFN-I, the question arises whether background production of IFN-I maintains the basal level of IL-15. In support of this idea, IFN-I receptor-deficient mice possess less than half the numbers of $CD122^{hi}$ MP $CD8^+$ T cells found in normal B6 mice, and there is even further depletion of $CD122^{hi}$ MP $CD8^+$ T cells in $STAT1^-$ mice (unpublished observations), which are unresponsive to both IFN-I and IFN-γ. If the background production of IFNs does indeed determine the basal level IL-15, the question then arises whether production of IFNs is endogenously regulated or depends on exposure to trace levels of exogenous mediators released from gut bacteria or other commensals.

One way to address whether stimuli from commensals are involved in homeostasis of memory $CD8^+$ T cells is to study mice with a defect in their ability to recognize microbial products, such as myeloid differentiation factor 88 $(MyD88)^-$ and Trif mutant mice (57–59). Interestingly, $CD122^{hi}$ MP $CD8^+$ T-cell numbers are partly reduced in Trif mutant mice but relatively normal in $MyD88^-$ mice (unpublished observations). The $CD122^{hi}$ MP $CD8^+$ T-cell numbers in mice with combined defect in both MyD88 and Trif have yet to be analyzed. An alternative approach to study the role of chronic stimulation from commensals is to analyze mice raised under completely germ-free conditions, which are devoid of microbial agents. The literature on T cells in germ-free mice is rather outdated, as careful analysis of T-cell subsets was not performed. Nonetheless, several groups have reported that the overall composition of the T-cell pool in germ-free mice is not significantly different from normal mice, indicating that MP cells do exist in germ-free mice (24, 25, 60). In support of this idea, recent analysis of germ-free and antigen-free mice (germ-free mice fed with low molecular weight food to minimize antigen exposure through food) confirmed the presence of near-normal numbers of MP cells, including $CD122^{hi}CD8^+$ T cells, in these mice (unpublished observations). The findings in germ-free mice are significant for two reasons. First, the basal levels of IL-15 (and possibly IFNs that induce IL-15 production) that are necessary to support MP $CD8^+$ T-cell survival can apparently be induced solely through endogenous mechanisms in the absence of signals from environmental or commensal antigens. Second, it follows that large numbers of MP cells can be generated through homeostatic mechanisms without exposure to foreign antigens. Hence, the interesting possibility arises that the bulk of MP cells formed in normal mice raised under conventional conditions are not true memory cells but arise through homeostatic mechanisms in response to self-antigens.

### Role of γc cytokines other than IL-15

Despite the fact that MP $CD8^+$ T cells are heavily dependent on IL-15 for survival, other γc cytokines are known to affect memory $CD8^+$ T-cell homeostasis. Here, IL-7 is of particular interest. Thus, MP $CD8^+$ T cells respond well to IL-7 *in vivo*, and increasing the level of IL-7 can overcome the requirement for IL-15, as shown by the large numbers of $CD122^{hi}$ MP $CD8^+$ T cells that arise when $IL\text{-}15^-$ mice are crossed to an IL-7 transgenic background (61). Similarly, MP $CD8^+$ T cells transferred to syngeneic irradiated hosts undergo efficient acute homeostatic proliferation in hosts lacking either IL-15 or IL-7 but fail to proliferate in hosts lacking both cytokines (62, 63). These findings suggest that the level of IL-7 found under normal conditions (and in $IL\text{-}15^-$ mice) is too low to be utilized by MP $CD8^+$ T cells, even though the level of IL-7 is sufficient to support survival of naïve T cells. The inability of MP $CD8^+$ T cells to utilize IL-7 is puzzling, considering that IL-7Rα levels on MP $CD8^+$ T cells are comparable to the levels on naïve T cells, and MP $CD8^+$ T cells can out-compete naïve T cells for IL-7 (62).

Why MP $CD8^+$ T cells display a strong bias for IL-15 over IL-7 is unclear, but this trait appears to be set by the priming conditions that induce the initial generation of MP cells. This notion stems from the observation that the nature of the immunogen determines the extent of IL-15 dependency for the induced memory $CD8^+$ T cells. Thus, immunization with protein antigens plus purified adjuvants, such as poly I:C or heat shock proteins, leads to the generation of memory $CD8^+$ T cells that are just as dependent on IL-15 as MP $CD8^+$ T cells (55). In contrast, memory $CD8^+$ T cells that are generated from immunization with infectious agents, such as lymphocytic choriomeningitis virus and *Listeria*, can survive for extended periods in the absence of IL-15 by relying on IL-7; nonetheless, these memory $CD8^+$ T cells do require IL-15 for background homeostatic proliferation and gradually disappear when deprived of IL-15 (64, 65). How the priming conditions establish the dependency for IL-7 versus IL-15 is not clear, but subtle differences in the induced expression levels of cytokine receptors may be important. Thus, in line with their observed cytokine dependency, memory $CD8^+$ T cells generated in response to non-infectious protein antigens express higher levels of CD122 but lower levels of IL-7Rα than memory $CD8^+$ T cells induced by infectious agents (unpublished observation).

Since homeostasis of memory $CD8^+$ T cells can involve IL-7 as well as IL-15, the question arises whether other γc cytokines have a similar function. A positive role for IL-2 on homeostasis of memory $CD8^+$ T cells is suggested by the finding that injection of IL-2 at the end of the primary immune response can prevent death of effector $CD122^{hi}$ $CD8^+$ cells (66). However, there is no evidence that IL-2 is required by these cells under normal conditions. On the contrary, IL-2 may play a suppressive role in homeostasis of memory $CD8^+$ cells. In support of this idea, injection of anti-IL-2 monoclonal antibody (mAb) was found to cause a marked increase in basal homeostatic proliferation of MP $CD8^+$ T cells (67). Since anti-IL-2 mAb is thought to neutralize circulating IL-2, it was proposed that anti-IL-2 mAb leads to the removal of IL-2-dependent $CD25^+CD4^+$ regulatory T cells (Tregs), which somehow suppress the activity of IL-15 (68). Subsequently, however, it was found that the effect of anti-IL-2 mAb on MP $CD8^+$ T-cell proliferation was IL-15 independent, which led to the suggestion that Tregs mediate their suppressive effect by blocking the activity of a novel IL-15-like cytokine (69). The puzzling effect of anti-IL-2 mAb on MP $CD8^+$ T cells now has a simple explanation (70). Contrary to the popular belief that anti-IL-2 mAb blocks the activity of IL-2, it has been recently found that anti-IL-2 mAbs enhance the *in vivo* biological activity of pre-existing IL-2 on memory $CD8^+$ T cells. This idea stemmed from the unexpected finding that anti-IL-2 mAb injection was ineffective in increasing proliferation of MP $CD8^+$ T cells in the absence of IL-2, namely in $IL\text{-}2^-$ hosts. The notion that anti-IL-2 mAb can boost the activity of IL-2 was confirmed by the finding that injecting a complex of anti-IL-2 mAb already bound to IL-2 induced much greater proliferation of MP $CD8^+$ T cells than injecting either anti-IL-2 mAb or IL-2 alone. This finding also applied to MP CD8 cells from $CD25^-$ mice, indicating that IL-2 plus mAb complexes signaled through CD122. Proliferation induced by IL-2 plus mAb complexes extended to all $CD122^{hi}$ cells, including antigen-specific memory $CD8^+$ T cells and NK cells.

The ability of cytokine/mAb complexes to boost biological activity extends to other γc cytokines, notably IL-4 and IL-7. Thus, as for IL-2, the activity of IL-4 and IL-7 *in vivo* is much improved when these cytokines are bound to specific mAb. For IL-15, a similar enhancement of activity occurs when IL-15 is bound to a soluble form of the IL-15Rα chain (unpublished observations by M. Rubinstein and authors). While these findings clearly indicate that several γc cytokines have the potential to regulate homeostasis of memory $CD8^+$ T cells, there is currently no evidence that normal MP $CD8^+$ T-cell homeostasis requires cytokines other than IL-15 and IL-7. This finding suggests that the availability of other cytokines is too low to be physiologically relevant under normal conditions. Nonetheless, it is still possible that IL-2 and IL-4 may play a role under conditions where these cytokines are produced in large amounts, for instance, during an active immune response.

As a side note, the mechanism by which mAb binding boosts the biological activity of cytokines is not known. Enhancing the half-life of cytokines in the circulation could be involved (71–73), but this explanation is clearly not the sole one. Rather, it seems that mAb alters the way the cytokine is presented to T cells, as removal of the Fc portion of the mAb [by producing $F(ab)_2^1$ fragments] neutralizes the boosting effect. What roles could the Fc portion of the mAb play? The most likely possibility is that cytokine/mAb complexes increase the effective concentration of the cytokine delivered to T cells by localizing cytokines onto the cell surface of $FcR^+$ cells, such as macrophages and dendritic cells. In addition, APCs may play an active role by prolonging the interaction of the cytokine with its receptor on T cells through interaction with adhesion molecules such as B7 and intercellular adhesion molecule. Engagement of these adhesion molecules could conceivably deliver costimulatory signaling to T cells and thereby intensify the signals mediated by the cytokine. The validity of these possibilities has yet to be tested.

### Homeostasis of $CD122^{lo}$ MP $CD8^+$ T cells

About 30% of MP ($CD44^{hi}$) $CD8^+$ cells in normal mice are $CD122^{lo}$ cells. These cells are IL-15 independent, as indicated by their presence in $IL\text{-}15^-$ mice and their selective survival when normal $CD44^{hi}$ $CD8^+$ T cells are transferred to $IL\text{-}15^-$ hosts (41, 43). Some $CD122^{lo}$ MP $CD8^+$ T cells may simply represent typical $CD122^{hi}$ cells that have downregulated CD122 expression following binding of IL-15. However, the bulk of $CD122^{lo}$ MP $CD8^+$ T cells differ from $CD122^{hi}$ cells in having a rapid turnover and displaying signs of activation, as manifested by a $CD69^{hi}CD62L^{lo}IL\text{-}7R\alpha^{lo}$ phenotype (unpublished data). These cells comprise nearly all of the few MP $CD8^+$ cells generated in $\gamma c^-$ mice and thus seem to be independent of γc cytokines. Recently, we have found that $CD122^{lo}$ MP $CD8^+$ T cells, unlike $CD122^{hi}$ cells, disappear rapidly following the transfer to MHC class $I^-$ mice. Hence, $CD122^{lo}$ MP $CD8^+$ T cells may be engaged in chronic responses to MHC class I ligands, presumably self-ligands. Interestingly, their dependency on TCR contact with MHC class I ligands is shared by memory $CD8^+$ T cells engaged in chronic responses to persistent viral infections (74). The

implication therefore is that both for self- and foreign antigens, continuous contact with antigen renders cells dependent on TCR signals and somehow prevents the cells from acquiring sensitivity to cytokines. Whether unresponsiveness to cytokines is simply a reflection of low expression of cytokine receptors or has some other explanation is still unclear.

### Memory $CD4^+$ T cells

The factors regulating homeostasis of memory $CD4^+$ T cells are less well understood than for memory $CD8^+$ T cells. Early studies suggested that memory $CD4^+$ T cells did not require contact with MHC class II for survival. Thus, it was found that *in vitro*-activated TCR transgenic $CD4^+$ T cells survived equally well upon adoptive transfer into normal versus MHC class $II^-$ hosts (34). These observations were corroborated by the subsequent finding that the pool size of naturally occurring MP $CD4^+$ T cells did not decline when the expression of TCR was abolished on mature T cells (12). Nonetheless, TCR ablation considerably reduced the basal rate of homeostatic proliferation of MP $CD4^+$ T cells, suggesting that MHC ligands do affect homeostasis of MP $CD4^+$ T cells (12). Additional support for this possibility came from a report demonstrating that while survival of TCR transgenic memory $CD4^+$ T cells did not require contact with MHC class II molecules, these cells failed to display the full range of effector functions (75). Moreover, another group found evidence that signaling through the TCR, presumably from contact with MHC, was essential for homeostasis of MP $CD4^+$ T cells but only in the absence of contact with IL-7 (76).

A likely explanation for this controversy is that MP $CD4^+$ T cells and antigen-specific memory $CD4^+$ T cells are not maintained by the same homeostatic mechanisms. This idea is supported by the finding that, as a population, MP $CD4^+$ T cells have about two to threefold faster rate of basal homeostatic proliferation than antigen-specific memory $CD4^+$ T cells (77, 78). Interestingly, the increased rate of proliferation is largely due to a minor subset of MP $CD4^+$ T cells that has a very rapid rate of turnover; this fast-dividing subset is easily observed in adoptive transfer experiments (62). The rapidly dividing cells are not $CD25^+$ Tregs or NKT cells, as depletion of these cells does not alter the proliferation rate of $CD44^{hi}$ MP $CD4^+$ T cells. In contrast to the fast-dividing population, the remaining MP $CD4^+$ T cells resemble antigen-specific memory $CD4^+$ T cells, in that these cells undergo only slow homeostatic proliferation (78, 79). Hence, MP $CD4^+$ T cells appear to be comprised of heterogeneous populations of cells. Also, unlike antigen-specific memory $CD4^+$ T cells, which are sustained at a low state of activation by homeostatic factors, it is possible that some MP $CD4^+$ T cells are maintained at a higher state of activation, because they are chronically stimulated by foreign antigens that cannot be eliminated, such as those that arise from commensal bacteria. In support of this idea, the fast-dividing population of MP $CD4^+$ T cells is not seen when MP $CD4^+$ T cells are adoptively transferred into totally MHC class $II^-$ mice, that is, mice that differ from 'conventional' MHC class $II^-$ mice in being unable to generate mixed H2-A$\alpha$/E$\beta$ heterodimers (80). It is also likely that a subset of MP $CD4^+$ T cells is generated solely from contact with self-antigens through homeostatic mechanisms, as suggested by the presence of MP cells in germ-free mice (24, 25). MP $CD4^+$ T cells generated through homeostatic mechanisms are likely to be maintained at a low state of activation with slow basal homeostatic proliferation, but confirming this idea will require analysis of MP $CD4^+$ T cells in germ-free mice.

Since a comparable subset of cells with a distinctly faster rate of turnover does not exist among MP $CD8^+$ T cells (62), the question arises why such a feature is restricted to MP $CD4^+$ T cells. This question has yet to be resolved but may reflect that exogenous antigens, such as commensal bacterial antigens, are much more efficiently presented by MHC class II molecules than class I molecules. Whatever the explanation, the presence of the fast-dividing subset of MP $CD4^+$ T cells may have a major impact on homeostasis of other T cells through competition for homeostatic factors. For instance, the gradual attrition of antigen-specific memory, which was reported to be specific for $CD4^+$ but not $CD8^+$ T cells (81), could be due to competition for resources from fast-dividing MP $CD4^+$ T cells. Also, the decline in numbers of naïve T cells with age could be partly caused by competition from the fast-dividing population of MP $CD4^+$ T cells, which is likely to increase proportionally in numbers along with the overall size of the MP T-cell pool.

As with other subsets of T cells, the most important homeostatic factors for MP $CD4^+$ T cells appear to be the $\gamma$c cytokines IL-7 and IL-15. Initially, $\gamma$c cytokines were thought to be irrelevant for these cells, because TCR transgenic $CD4^+$ T cells that developed in a $\gamma c^-$ background displayed a very short lifespan as naïve cells but survived efficiently after converting into memory cells (82). A caveat of this study is that $\gamma c^-$ memory $CD4^+$ T cells may have acquired the ability to survive through an abnormal pathway during their development, especially during differentiation in the thymus. We initially concluded that IL-7 and IL-15 were not needed for homeostasis of memory $CD4^+$ T cells based on the finding that the fraction of fast-dividing MP $CD4^+$ T cells did not

require either IL-7 or IL-15 for their proliferation (62). As discussed above, however, we now believe that these rapidly dividing cells are probably chronically driven by foreign (or self) antigens and do not represent typical resting memory $CD4^+$ T cells. Since memory $CD4^+$ T cells express high levels of CD127 but low levels of CD122, it was thus not surprising when subsequent studies found an essential role for IL-7 on homeostasis of memory $CD4^+$ T cells. Here, one study found that in the absence of any TCR signaling, that is, when inducible TCR signaling was turned off, MP $CD4^+$ T cells were heavily dependent on IL-7 for survival and homeostatic proliferation (76). For antigen-specific memory $CD4^+$ T cells, IL-7 dependency was evident even with intact TCR signaling capacity. Thus, OT-II TCR transgenic memory $CD4^+$ cells, which are unable to undergo homeostatic proliferation, were found to be heavily dependent on IL-7 for survival (83). Moreover, injection of mAb specific for IL-7R resulted in a significant reduction in survival and background turnover rate of *de novo*-generated polyclonal antigen-specific memory $CD4^+$ T cells (78).

Because $CD4^+$ T cells have low CD122 expression and are generated normally in IL-$15^-$ mice, IL-15 has been considered to be unimportant for homeostasis of memory $CD4^+$ T cells. Nonetheless, human and monkey memory $CD4^+$ T cells are known to respond readily to IL-15 (84, 85), and mice over-expressing transgenic IL-15 were found to display enhanced $CD4^+$ T-cell responses to infection by pathogens (86). Moreover, the low but significant level of CD122 expression on mouse memory $CD4^+$ T cells is about the same as for naïve $CD8^+$ T cells (39), which are reduced in number in IL-$15^-$ mice and therefore are partly dependent on IL-15 for survival (43). Collectively, these findings suggest at least some role for IL-15 on homeostasis of memory $CD4^+$ T cells. In fact, a recent study on *de novo*-generated polyclonal antigen-specific memory $CD4^+$ T cells found that IL-15 did have a mild but significant effect on supporting background cell turnover (78). Since polyclonal memory $CD4^+$ T cells may be 'contaminated' with chronically activated MP $CD4^+$ T cells, it became important to assess the homeostatic requirement of TCR transgenic memory $CD4^+$ T cells. Using a particular line of TCR transgenic cells (SMARTA) that shows significant background homeostatic proliferation, we recently found that while IL-7 is essential for survival of these cells, both IL-7 and IL-15 have equal roles in driving background homeostatic proliferation in normal T-sufficient hosts (unpublished observation).

## Conclusions

There is now little doubt that homeostasis of memory T cells is largely controlled by the γc cytokines IL-7 and IL-15. Although these cytokines do display overlapping functions, IL-7 appears to be primarily important for maintaining cell survival, whereas IL-15 is necessary to drive homeostatic proliferation. This applies especially to memory $CD8^+$ T cells while for memory $CD4^+$ T cells IL-7 seems to play a more conspicuous role than IL-15. It is becoming increasingly clear that spontaneously generated MP cells, as a population, do not display exactly the same homeostatic requirements as true memory cells. Since MP cells appear to be heterogeneous, a better approach for identifying the relevant subsets within MP cells will be required to use these cells as representatives of antigen-specific memory cells. Future studies on homeostasis may focus on the key questions of how naïve and memory T cells can coexist while being dependent on the same two cytokines and how the production of these cytokines is maintained and regulated. This knowledge could be very useful in devising approaches for restoring T-cell populations after acute lymphodepletion, for example, after BM transplantation and in replacing T cells in old age.

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