Overexpression of Interleukin (IL)-7 Leads to IL-15–independent Generation of Memory Phenotype CD8⁺ T Cells

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Abstract

Transgenic (TG) mice expressing a high copy number of interleukin (IL)-7 cDNA under the control of the major histocompatibility complex (MHC) class II promoter display a 10–20-fold increase in total T cell numbers. Here, we show that the increase in T cell numbers in IL-7 TG mice is most apparent at the level of memory phenotype CD44hi CD122hi CD8⁺ cells. Based on studies with T cell receptor (TCR) TG mice crossed to IL-7 TG mice, increased levels of IL-7 may provide costimulation for TCR recognition of self-MHC ligands and thus cause naive CD8⁺ cells to proliferate and differentiate into memory phenotype cells. In addition, a marked increase in CD44hi CD122hi CD8⁺ cells was found in IL-7 TG IL-15⁻/⁻ mice. Since these cell are rare in normal IL-15⁺/⁺ mice, the dependency of memory phenotype CD8⁺ cells on IL-15 can be overcome by overexpression of IL-7.

Key words: T lymphocytes • homeostasis • cytokines • mice • transgenic

Introduction

The overall size and composition of the mature T cell pool are closely regulated by homeostatic mechanisms (1). Recently, it has been shown that homeostasis of naive T cells is primarily controlled through TCR contact with self-MHC/peptide ligands and exposure to the cytokine IL-7 (2–5). Thus, in the absence of interaction with either of these ligands, naive T cells disappear and fail to undergo “homeostatic” proliferation in T cell–deficient conditions (2–5). Since the density of self-MHC/peptide ligands is constant, IL-7 may be the key factor in determining the overall size of the naive T cell pool. Accordingly, overproduction of IL-7 would presumably lead to a proportional enlargement of the naive T cell pool. In contrast to naive cells, homeostasis of memory T cells is known to be regulated independently of contact with MHC molecules (6, 7). In terms of cytokine requirements, none of the common γ chain (γc)* family of cytokines (IL-2, -4, -7, -9, -15) appears essential for memory CD4⁺ cells (8). By contrast, memory CD8⁺ cells are heavily dependent on IL-15 (9, 10). Thus, most memory CD8⁺ cells express elevated levels of the IL-15R CD122, undergo selective proliferation in response to IL-15, and are markedly depleted in IL-15⁻/⁻ and IL-15Rα⁻ mice (9–12).

IL-7 was initially described as a growth factor for B cell progenitors and was shown to be produced by bone marrow stromal cells (13). Subsequent studies showed that IL-7 is also synthesized by other tissues, including thymic and intestinal epithelial cells (14, 15). Furthermore, a generation of IL-7⁻/⁻ and IL-7R⁻/⁻ mice revealed that IL-7 has a nonredundant role in supporting early development of both B and T cells (16, 17). In addition to knockout mice, four independent lines of transgenic (TG) mice overexpressing IL-7 were generated in the early 1990s (18–21). Although most of the TG mice were found to possess increased numbers of B and T cells, a careful examination of the T cell pool was not performed.

To study the effect of IL-7 overproduction on T cell homeostasis, we analyzed a B6 TG line that expresses a high copy number of IL-7 cDNA under the control of the MHC class II promoter (21). Despite a marked (25–50-fold) elevation in IL-7 levels, these mice appear healthy.
Materials and Methods

Mice. IL-7 TG mice (21) were obtained from J. Andersson at the Basel Institute and maintained by breeding to C57BL/6 (B6) or B6.Ly 5.1+ mice. All mice used in the current study were hemizygous for the transgene. B6 and B6.PL congenic mice were purchased from The Scripps Research Institute (TSRI) breeding facility. Origins of OT-I, HY, IL-15−, and β2m−K−D− mice were described previously (3, 5).

FACS® Analysis. Suspensions of thymus, LN, and spleen cells were double- and triple-stained as described previously (2) using various combinations of PE-anti-CD44, PE-anti-CD122, Cy5-anti-CD8, FITC-anti-CD8, Cy5-anti-CD4, Cy5-anti-ly 5.1, and biotinylated T3.70 (all from eBioscience). Biotinylated anti–Thy-1.1, anti–γc and FITC-Vβ5, and PE-Vα2 antibodies were purchased from BD PharMingen. Biotinylated mAbs were detected with Cy5-conjugated streptavidin (Jackson ImmunoResearch Laboratories).

For intracellular cytokine staining, spleen cells (4 × 10⁵ cells per milliliter) in complete medium containing 0.67 μg/ml Brefeldin A (GolgiStop; BD PharMingen) were incubated for 7 h in 24-well plates coated with anti-CD3 (2C11; eBioscience) mAb (0.5 μg/ml) and stained as described previously (22). Briefly, cells were first stained with Cy5-anti-CD8 and PE-anti-CD44, fixed with paraformaldehyde followed by permeabilization with saponin and stained with FITC-anti–IFN-γ mAb (eBioscience).

To assess homeostatic proliferation, small numbers (10⁶ cells per mouse) of FACS®-sorted CD44hi CD8+ cells were labeled with CFSE (Molecular Probes) and injected into mice exposed to 600 cGy irradiation and analyzed 7 d later as described previously (2).

The rate of background T cell turnover in adult thymectomized mice was performed by adding BrdU (0.8 mg/ml) into the drinking water for 7 d and staining LN cells as described previously (2).

Effect of cytokines in vitro was assessed by culturing CD44+ and CD8+ cells (2 × 10⁶ cells per milliliter), purified as described previously (2), for 5 d in complete medium containing IL-7 and/or IL-15 at 20 ng/ml. Some cultures contained mAbs to IL-7R (A7R34) (24) and IL-2R (TM-B1) (25) at 50 μg/ml. The in vivo effect of blocking IL-7R was measured by injecting mice intraperitoneally with either 200 μg of salt-precipitated A7R34 ascites or 200 μg of rat IgG every other day over a 7-d period. In vitro–cultured cells and LN and spleen cells from antibody-injected mice were analyzed by triple staining with FITC-anti-CD4, Cy5-anti-CD8 and PE-anti-CD44, or PE-anti-CD122 mAbs.

CDR3 Lengths Analysis of TCR Chains. Spectratyping of TCR-Vα and -Vβ repertoire was performed on purified CD4+ and CD8+ cells as described previously (26). Briefly, after cDNA synthesis from total RNA, the RNA was denatured and reverse transcribed. Small aliquots of the cDNA were amplified by PCR using primers previously described to analyze the repertoire of Vα and Vβ chains (27). The PCR product was then subjected to run-off reaction with fluorescent-tagged primers and analyzed by capillary electrophoresis in an automated DNA sequencer (Applied Biosystems) and the distribution of CDR3 lengths determined.

Results and Discussion

Characterization of T Cells in IL-7 TG Mice. As reported previously (21), young adult IL-7 TG mice were found to contain massive numbers of T (and B) cells (10–20 times above normal) in the secondary lymphoid tissues, despite the presence of a relatively normal sized thymus (Fig. 1 A). The increase in peripheral T cell numbers was more pronounced for CD8+ cells than CD4+ cells and resulted in a reduction in the CD4/CD8 ratio. The increase in total T cell numbers and the preferential effect of IL-7 on CD8+ cells are likely to be a consequence of IL-7 acting directly on mature T cells as similar effects were observed in normal mice given repeated injection of recombinant IL-7 (28–

Figure 1. Characterization of T cells in young adult IL-7 TG mice. (A) T cell subset distribution and cell numbers in the thymus, LN, and spleen in IL-7 TG and LMs. Cells were triple-stained for CD4, CD8, CD44, or CD122 and analyzed by flow cytometry as described in Materials and Methods. Total numbers of thymocytes and indicated naive and memory phenotype CD4+ and CD8+ cells, combined from spleen and pooled LN s, IL-7 TG, and LMs are shown. Data are representative of >20 TG and LM mice. (B) Expression of CD44 and CD122 on gated LN CD4+ and CD8+ cells from IL-7 TG and LMs. (C) Randomly distributed CDR3 lengths of TCR-Vα chains expressed on CD8+ cells from IL-7 TG mice. CDR3 lengths on most Vα chains were determined on purified CD8+ cells from IL-7 TG and LM mice as described in Materials and Methods. Representative data for indicated Vα chains are shown; all analyzed chains were randomly distributed in both TG and LM mice.

and, unlike other lines (18, 20), remained free of dermatitis (21); tumor formation is low and restricted to B cells. Here, we show that the massive overproduction of T cells in IL-7 TG mice is largely skewed to memory-phenotype CD44hi CD122hi CD8+ cells. Based on the results of crossing IL-7 TG mice to TCR TG and IL-15− mice, IL-7 may play an important role in guiding both the generation and maintenance of memory CD8+ cells.
tion of IFN-γ in vitro stimulation with anti-CD3 mAb, the proportion of IFN-γ synthesizing cells was much higher for TG CD44hi cells (49%) than for normal B6 CD44hi cells (9%) (Fig. 3 D). Since IL-7 has costimulatory activity for T cell stimulation and function (30, 31), this difference could be a reflection of prior exposure of the TG cells to high levels of IL-7 in vivo.

Generation of TCR TG CD44hi CD8+ Cells in IL-7 TG Mice. T cells with a memory phenotype usually originate from naive T cells responding to foreign antigen, but can also arise from naive T cells undergoing homeostatic proliferation to self-ligands (32). To examine which ligands, self or foreign, cause production of memory phenotype CD8+ cells in IL-7 TG mice, we crossed two TCR TG lines, OT-I and HY, to IL-7 TG mice.

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Figure 2. CD44hi CD8+ cells from IL-7 TG mice functionally resemble CD44hi CD8+ cells from wild-type mice. (A) Background turnover of T cells IL-7 TG mice. Adult thymectomized IL-7 TG and LMs were given BrdU in the drinking water for 7 d and LN cells were triple stained for BrdU, CD4, and either CD4 or CD8 as described in Materials and Methods. (B) IL-7 TG CD44hi CD8+ cells undergo the same rate of homeostatic proliferation in T cell-depleted hosts as wild-type CD44hi CD8+ cells. CD44hi CD8+ cells from Ly 5.1+ IL-7 TG and LM mice purified by cell sorting were CFSE labeled and injected into irradiated (600 cGy) B6 mice. 7 d after transfer donor cells in host LN were analyzed for CFSE expression by staining for Ly5.1+ and CD8+. Shown are gated donor LMs and TG CD8+ cells. (C) Homeostatic proliferation of IL-7 TG CD44hi CD8+ cells is MHC independent. Sorted and CFSE-labeled CD44hi CD8+ cells from Ly 5.1+ IL-7 TG mice were injected into irradiated B6 and MHC class I- knockouts (B2m−/−) mice and analyzed 7 d later as in B. (D) IL-7 TG CD44hi CD8+ cells synthesize IFN-γ upon activation. Spleen cells from IL-7 TG and LMs were stimulated with anti-CD3 mAb in vitro for 7 h in the presence of Brefeldin A and stained for CD8, CD44, and intracellular IFN-γ as described in Materials and Methods. Shown are gated CD8+ cells. All data are representative of results from three experiments.
For the OT-I line, nearly all (~95%) of the CD8⁺ cells in this line are clonotype-positive (Vα2⁺ Vβ5⁺) cells and have a naive CD44lo phenotype (data not shown). These naive cells appear to have significant affinity for self-MHC/peptide ligands because exposure to these ligands after transfer to T cell-depleted hosts causes strong homeostatic proliferation of the cells and a switch to a memory phenotype (3). When OT-I mice were crossed to IL-7 TG mice, thus producing OT-I IL-7 TG mice, total numbers of CD8⁺ cells in these mice were increased about threefold relative to OT-I LMs that lacked the IL-7 transgene (Fig. 3). Significantly, numbers of CD44int CD8⁺ cells were ~20-fold higher in OT-I IL-7 TG mice than in normal OT-I LMs. In addition, in contrast to OT-I LMs, many of the “CD44int/hi” cells in OT-I IL-7 TG mice were actually CD44int rather than CD44hi (Fig. 3). This finding is of interest because OT-I cells show a similar CD44int/hi phenotype after homeostatic proliferation in T cell-depleted hosts (3). Since nearly all (~95%) of the CD8⁺ cells in OT-I IL-7 TG mice were Vα2⁺ Vβ5⁺, therefore, it would seem highly likely that the stimulus for expansion of CD44int/hi cells in these mice was provided by self-MHC/peptide ligands rather than foreign antigens. Thus, the implication is that high levels of IL-7 in OT-I IL-7 TG mice act as a costimulator to drive naive OT-I cells to undergo proliferation and differentiation in response to self-MHC/peptide ligands. Despite the high penetrance of the OT-I transgene, however, one caveat is that the IL-7 TG OT-I mice were not in a background (recombination activating gene [RAG]⁻ or TCR-α⁻) that precludes expression of endogenous TCR chains. Therefore, the contribution of foreign antigens in upregulation of CD44 cannot be totally excluded.

If self-MHC/peptide ligands are driving production of CD44hi CD8⁺ cells in IL-7 TG mice, the capacity of high levels of IL-7 to augment T cell reactivity to self-MHC/peptide ligands might not apply to T cells with “below average” affinity to self-ligands. To assess this possibility we examined the HY TCR TG line. As shown previously, the TCR clonotype-positive cells in this line (detected by T3.70 mAb) fail to undergo homeostatic proliferation in T cell-depleted hosts (2), presumably because the TCR affinity of T3.70⁺ cells for self-ligands is quite low. HY T cells do undergo homeostatic proliferation but this applies only to the T3.70⁻ subset (2). As shown in Fig. 3, HY IL-7 TG mice showed a marked expansion of CD44hi CD8⁺ cells. Significantly, almost all of these cells were T3.70⁺; there was no expansion of T3.70⁺ cells and these cells retained a naive CD44lo phenotype. Thus, expansion of T3.70⁻ but not T3.70⁺ cells in HY IL-7 TG mice correlated closely with the capacity of T3.70⁻ but not T3.70⁺ cells to undergo homeostatic proliferation in T cell-depleted hosts.

Collectively, these data on OT-I and HY mice suggest that a significant proportion of the expanded CD44hi CD8⁺ cells in IL-7 TG mice are derived from precursor cells stimulated by self-MHC/peptide ligands. This notion is consistent with the finding that the TCR repertoire of CD8⁺ cells appears very diverse (Fig. 1 C). In addition, however, a proportion of the expanded CD44hi CD8⁺ cells may arise through the action of IL-7 on naive CD8⁺ cells responding to foreign antigens. In this respect, we have observed that IL-7 has marked costimulatory activity for T cells responding to foreign antigens in vivo. Thus, injection of male splenic APC into IL-7 TG HY mice led to much greater expansion of T3.70⁺ cells followed by establishment of a large pool of T3.70⁺ memory CD44hi CD8⁺ cells than was observed in HY mice lacking IL-7 transgene (data not shown). Although the relative contribution made by foreign versus self-antigens in the production of CD44hi CD8⁺ cells in IL-7 TG mice is unknown it is notable that the marked increase in CD44hi CD8⁺ cell numbers in these mice is apparent even in neonatal (1.5 wk) mice (data not shown). With high IL-7 levels, CD44hi CD8⁺ cells arise very early in life and accumulate progressively.

**IL-15–Independent Generation of CD44hi CD8⁺ Cells in IL-7 TG Mice.** As mentioned earlier (see Introduction), survival of most CD44hi CD8⁺ cells in T cell–sufficient mice has recently been shown to be heavily dependent on IL-15 (9–11). IL-15 dependency is particularly pronounced for CD122⁺ CD44hi CD8⁺ cells, as these cells are conspi-
uous absence in IL-15− mice (unpublished data). To determine whether the generation and/or the maintenance of CD44hi CD8+ cells in IL-7 TG mice is IL-15 dependent, IL-7 TG mice were crossed with IL-15− mice. Surprisingly, comparison of 4-wk-old IL-15− IL-7 TG mice with age-matched control IL-15+ IL-7 TG LMs revealed that IL-15 is dispensable for generation of CD122hi CD44hi CD8+ cells in IL-7 TG mice. Thus, in terms of both total cellularity and phenotype, including both CD44 and CD122 expression, the peripheral CD8+ cell compartment was comparable in IL-15+ IL-7 TG versus IL-15− IL-7 TG mice (data not shown). It should be mentioned that IL-15 deficiency was accompanied by a slight reduction in the total number of CD8+ cells and a minor increase in the total number of CD4+ cells (Fig. 4). The point to emphasize, however, is that numbers of IL-15 responsive CD122hi CD8+ cells rose from nearly undetectable levels in IL-15− mice to very high levels in IL-7 TG IL-15− mice (Fig. 4).

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**Figure 4.** IL-15 is not required for generation of CD44hi CD8+ cells in IL-7 TG mice. LN cells from young adult IL-7 TG mice bred to an IL-15− background were stained for CD4, CD8, and CD44 or CD122 and analyzed. Shown are histograms of CD44 and CD122 on gated CD4+ and CD8+ cells as compared with the same cells from age-matched control LMs, IL-7 TG, and IL-15− mice. Total numbers of CD4+, CD8+, and CD122hi CD8+ cells from spleen and LNs from the mice are shown below. Data are representative of results from six to eight individuals for each type of mice.

Since non-TG IL-15− mice are virtually devoid of CD122hi CD8+ cells (reference 11 and Fig. 4), the above finding with IL-7 TG IL-15− mice indicates that high concentrations of IL-7 can compensate for absence of IL-15 in promoting survival of CD44hi CD122hi CD8+ cells. In support of this idea, a subitogenic dose (20 ng/ml) of either IL-7 or IL-15 maintained viability of CD44hi CD8+ cells in vitro for 5 d, whereas these cells died in the absence of cytokines (Fig. 5 A). This finding applied equally to T cells purified from IL-7 TG or wild-type mice. Whereas IL-7 was also able to enhance survival of other T cell subsets, the antiapoptotic function of IL-15 was largely restricted to CD44hi CD8+ cells, presumably because the IL-15 receptor, CD122, is expressed at a much higher level on CD44hi CD8+ cells than on other T cell subsets (9).

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**Figure 5.** Role of IL-7 in supporting survival of CD44hi CD8+ cells in vitro and in vivo in IL-7 TG mice. (A) IL-7 can maintain survival of CD44hi CD8+ cells in vitro. Aliquots of purified IL-7 TG LN T cells were incubated with the indicated cytokines at (20 ng/ml) either alone or in the presence of anti-IL-7Rα mAb (A7R34), anti-CD122 mAb (TM-β1), or both mAbs at 50 μg/ml. The cells were harvested 5 d later and stained for CD4, CD8, and CD44, and the numbers of viable CD44hi CD8+ cells were calculated. (B) Blocking the IL-7R leads to depletion of CD44hi CD8+ cells in IL-7 TG mice. Groups of two to three LMs, IL-7 TG, and IL-15− IL-7 TG mice were injected three times with either 200 μg of anti-IL-7Rα mAb (A7R34) or rat IgG at 2-d intervals. 2 d after the last injection, LN and spleen cells were collected and stained for CD4, CD8, and CD44. The total numbers of CD44hi CD8+ cells recovered from spleen and pooled LN are shown. Another experiment showed similar results.
Although IL-7 is presumed to mediate its effect through the IL-7R, it is conceivable that the high levels of IL-7 available in IL-7 TG mice might act through weak cross-reactive binding to the IL-15R. This possibility seems unlikely for two reasons. First, the capacity of IL-7 to rescue CD44hi CD8+ cells from spontaneous death in vitro was strongly inhibited by anti–IL-7Rα mAb, and the presence of anti–CD122 mAb did not diminish the effect of IL-7 (Fig. 5 A). This finding also applied when the concentration of IL-7 was raised to a high level (data not shown). Second, injecting either IL-7 TG or IL-15−/− IL-7 TG mice for 1 wk with anti–IL-7Rα mAb (200 μg every other day) caused a marked reduction in total numbers of CD44hi CD8+ cells in the mice (Fig. 5 B). A partial reduction in CD44hi CD8+ cells numbers was also observed in control LM mice (Fig. 5 B). The reduction in cell numbers in these mice is unlikely to be due to antibody-mediated opsonization as depletion of other IL-7Rhi cells, e.g., CD44hi CD4+ cells and mature B cells, was minimal (data not shown).

Our observation that the elevation of T cell numbers in IL-7 TG mice is skewed toward CD8+ cells is consistent with prior evidence on the effects of short-term injection of IL-7 into normal mice (28–30). Although these latter data indicated that IL-7 acted largely on peripheral T cells (rather than thymocytes), the issue of whether IL-7 stimulated naive T cells or memory T cells or both subsets was not resolved. The data in this paper suggest that, in IL-7 TG mice, elevated levels of IL-7 boost homeostasis of memory CD8+ cells through two different mechanisms.

First, the data on IL-7 TG TCR TG mice suggest that high levels of IL-7 amplify TCR recognition of self-MHC ligands by naive CD8+ cells. For these cells, TCR recognition of self-ligands in the presence of background levels of IL-7 normally induces a covert signal that is sufficient to keep naive CD8+ cells alive, but without inducing proliferation or a change in surface phenotype. With high levels of IL-7, however, TCR signaling is enhanced and contact with self-ligands causes naive CD8+ cells to proliferate and differentiate into memory phenotype cells.

Second, the high levels of IL-7 contribute to survival and turnover of established memory phenotype CD8+ cells. As discussed earlier, the background turnover and survival of CD44hi CD8+ cells is normally controlled by IL-15; IL-7 is not important, probably because levels of IL-7 in the peripheral lymphoid tissues of normal mice are too low to play a significant role in homeostasis. However, in IL-7 TG mice one can envisage that IL-7 and IL-15 both contribute to homeostasis. The presence of large numbers of CD44hi CD122hi CD8+ cells in IL-15−/− IL-7 TG mice but not normal IL-15−/− mice is then readily explained. Here, high levels of IL-7 compensate for the lack of IL-15 and homeostasis of CD44hi CD8+ cells remains normal. The finding that the total numbers of CD44hi CD8+ cells in IL-15−/− IL-7 TG mice dropped sharply after treatment with anti–IL-7R mAb is consistent with this idea. However, the finding that anti–IL-7R mAb treatment had a similar effect on IL-15+/− IL-7 TG mice is surprising because here we expected the cells to be rescued by IL-15. It is conceivable, however, that the massive overproduction of CD122hi CD8+ cells in IL-7 TG mice depletes IL-15, thus causing the cells to be heavily dependent on IL-7.

In addition to memory phenotype CD8+ cells, IL-7 TG mice clearly contain increased numbers of naive T cells, including both CD4+ and CD8+ cells. Likewise, naive T cell increase in number after injection of IL-7 (28–30). How IL-7 leads to expansion of naive T cells is unknown, although increases in cell survival, proliferation, and release of new T cells from the thymus are all likely possibilities. Resolving this important issue will have to await further investigation.

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