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REVIEW

T cell homeostasis

Jonathan Sprent[1], Jae-Ho Cho[1], Onur Boyman[2] and Charles D Surh[3]

The pool of mature T cells comprises a heterogeneous mixture of naive and memory CD4$^+$ and CD8$^+$ cells. These cells are long lived at a population level but differ markedly in their relative rates of turnover and survival. Here, we review how contact with exogenous stimuli, notably self MHC ligands and various γ_c cytokines, plays a decisive role in controlling normal T cell homeostasis.

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Typical CD4$^+$ and CD8$^+$ cells expressing αβ T cell receptors (TCR) form a pool of long-lived cells that recirculate continuously between blood and lymph through defined areas of the secondary lymphoid tissues (spleen, lymph nodes (LN) and Peyers patches).[1–5] On the basis of their surface markers, mature CD4$^+$ and CD8$^+$ T cells each comprise two broad subsets of cells. In young animals, most T cells are immunologically naive and, in mice, these cells characteristically show low levels of CD44. Such CD44^{lo} cells are resting cells and rarely, if ever, divide. The other subset of T cells has a CD44^{hi} phenotype and represents the progeny of naive T cells engaged in immune responses. These primed T cells have a more rapid rate of turnover than naive cells and carry immunological memory. CD44^{hi} memory T cells form only a small proportion (10–20%) of T cells in young mice but become a dominant population in old age. Most CD44^{hi} cells are presumed to be the descendants of cells responding to various environmental antigens and are termed 'memory-phenotype' (MP) cells. The possibility that some MP cells are the progeny of cells responding to self antigens will be discussed later.

In recent years, it has become apparent that T cell survival and turnover are shaped by complex homeostasis mechanisms. These mechanisms are distinctly different for naive and MP cells and are briefly reviewed below.

NAIVE T CELLS

The resting status and phenotype of naive T cells are largely a consequence of their prior contact with major histocompatibility complex (MHC) ligands in the thymus, MHC I for CD8$^+$ cells and MHC II for CD4$^+$ cells. As discussed elsewhere, intrathymic TCR contact with MHC ligands is crucial for determining which particular T cells are suited for export to the peripheral lymphoid tissues.[6] A small proportion (about 1%) of thymocytes have dangerously high affinity for self MHC ligands and these overtly auto-aggressive cells are destroyed *in situ* by a process of negative selection, a consequence of strong TCR signalling. Most thymocytes (around 98%) have negligible affinity for the MHC ligands expressed in the thymus and these cells undergo 'death by neglect' as the result of their failure to receive a TCR signal. Other thymocytes have weak but significant MHC affinity. These cells receive a correspondingly weak TCR signal that serves to rescue the cells from death by neglect, thereby causing the cells to survive and migrate to the periphery, a process termed positive selection. Because of extensive MHC polymorphism, only about 1% of thymocytes in any one individual have the appropriate physiological specificity for the particular self MHC ligands expressed in that individual. The remaining cells are a reserve pool and have the potential to undergo positive selection in thymuses expressing other MHC molecules.

As a result of positive selection, the T cells that populate the peripheral lymphoid tissues display strong reactivity to a wide spectrum of foreign antigens, but are largely tolerant of self antigens, especially ubiquitous self antigens. Tolerance to tissue-specific antigens is incomplete but, if they occur, responses to the latter are usually suppressed by CD4$^+$ CD25$^+$ T regulatory cells (T_{regs}), thus avoiding autoimmune disease.[7,8] In the case of ubiquitous self antigens, it is notable that positive selection induces upregulation of CD69 on responding thymocytes, implying overt activation of these cells.[6] CD69 expression on the selected cells is transient, however, and the cells become quiescent within a few days of export from the thymus. This transition from activated to resting cells is thought to reflect a process of TCR desensitization or 'tuning', thereby augmenting unresponsiveness to self ligands.[9–11]

Up to puberty, the size of the recirculating lymphocyte pool is proportional to body weight, resulting in a progressive increase in the T cell pool size from infancy to early adult life.[1–6] The thymus shrinks after puberty and becomes markedly atrophic by late middle age. Since thymic output is proportional to thymic mass, T cell production is thus maximal in young life and then declines progressively with age.

[1]Immunology and Inflammation Program, Garvan Institute of Medical Research, Darlinghurst, New South Wales, Australia; [2]Division of Immunology and Allergy, University Hospital of Lausanne, CHUV, Lausanne, Switzerland and [3]Department of Immunology, The Scripps Research Institute, La Jolla, CA, USA
Correspondence: Professor J Sprent, Garvan Institute of Medical Research, 384 Victoria St, Darlinghurst, New South Wales, 2010, Australia.
E-mail: j.sprent@garvan.org.au
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Throughout this period, however, the cellularity of the spleen and LN remains relatively constant. Recirculating naive T cells encounter self-MHC ligands continuously in these organs but, because of post-selection TCR tuning, the cells remain quiescent. It might seem to follow that naive T cells simply ignore self-ligands in the extrathymic environment and restrict their TCR reactivity to foreign antigens. Interestingly, this is not the case because depriving T cells from TCR contact with self-MHC ligands causes naive cells to gradually die.[12–14] The implication therefore is that continuous TCR contact with self ligands induces a form of covert signalling that promotes cell survival, presumably by maintaining the expression of Bcl-2 and other anti-apoptotic molecules. In addition, however, naive T cells also need to make contact with a cytokine, IL–7.[15,16] Thus, as for MHC ligands, depriving naive T cells from contact with IL-7 causes the cells to die. Hence, maintaining naive T cells in interphase for prolonged periods *in vivo* requires a combination of TCR interaction with self-MHC ligands plus exposure to IL-7.

Although T cell reactivity to self-MHC ligands is normally covert, minor changes in the lymphoid microenvironment can cause T cells to break tolerance and mount overt responses to self. This happens when total T cell numbers are reduced to a low level. Under these conditions, residual naive T cells begin to proliferate and expand, a process termed 'homeostatic proliferation' or 'lymphopenia-driven proliferation'.[17–25]

Homeostatic proliferation of naive T cells is most easily studied by transferring small numbers of these cells into congenitally T-deficient mice such as RAG$^{-/-}$, SCID or nude mice. In these hosts the donor T cells proliferate slowly, switch to a CD44^{hi} memory phenotype and gradually expand, thereby eventually expanding the total T cell pool to near-normal size. Such proliferation and expansion fails to occur in MHC$^{-/-}$ hosts, indicating that homeostatic proliferation is TCR dependent.[12,19] Significantly, proliferation is also abolished in IL-7$^{-/-}$ hosts.[15,16] Hence, the stimuli required for homeostatic proliferation in T-depleted hosts are apparently the same as for maintaining T cell survival in interphase in normal mice. So, why does T depletion initiate cell division? The answer to this puzzle is that reducing T cell numbers to a low level causes the background concentration of IL-7 to increase significantly.[26] The elevated level of IL-7 together with continuous TCR/MHC interaction then augments intracellular signalling and pushes T cells out of interphase and into cell division.

Homeostatic proliferation is typically slow with most cells dividing only 1–5 times over a period of 1–2 weeks; proliferation tends to be more pronounced for CD8$^+$ cells than CD4$^+$ cells. Generation of effector cell function is limited and after slow expansion over a period of several weeks the cells revert to resting cells with the features of typical CD44^{hi} central memory cells. These kinetics differ sharply from the response to foreign antigens. Here, proliferation is rapid and leads to prominent production of effector cells followed by wide scale death of most of these cells, only a small proportion of the cells surviving to form memory cells. As for the response to foreign antigens, homeostatic proliferation is directed largely to MHC ligands expressed on dendritic cells.[27,28] However, one notable difference between these two types of proliferation is that homeostatic proliferation does not seem to need costimulation. Thus, in marked contrast to T cell responses to foreign antigens, homeostatic proliferation does not require B7-CD28, CD40-CD40L or 4-1BB-4-1BBL interactions.[29] Another unique feature of homeostatic proliferation is that the response is polyclonal and applies to most, though not all TCR transgenic lines.[19,30] The prevailing view here is that the response is directed largely to MHC-associated ubiquitous self peptides, the intensity of the response reflecting the intrinsic TCR affinity of the responding cell for these ligands.[30] However, it should be mentioned that a small proportion of the cells proliferating in T-depleted hosts proliferate rapidly and are IL-7 independent but costimulation dependent.[19,31–33] This component of the response is much less prominent in germ-free hosts and appears to be directed to antigens from commensal bacteria.[33]

As discussed earlier, typical homeostatic proliferation in T-depleted hosts is controlled by IL-7, a member of the γ_c family of cytokines;[34] this family also includes IL-2, IL-4, IL-9, IL-15 and IL-21. One of these cytokines, IL-2, plays a crucial role in sustaining T_{regs} whereas, as considered later, another cytokine, IL-15, controls the survival and turnover of MP T cells. For naive T cells, these latter cytokines do not play an obvious role in homeostatic proliferation because, as mentioned above, proliferation is almost undetectable in IL-7$^{-/-}$ hosts. Hence, cytokines such as IL-2 and IL-15 cannot compensate for a lack of IL-7. Nevertheless, when in excess, these two cytokines induce strong proliferation of naive T cells, especially CD8$^+$ cells.[35,36] Such proliferation is apparent when mice are injected with exogenous IL-2 or IL-15. With injection of these cytokines into normal mice, proliferation is largely restricted to MP CD8$^+$ cells and NK cells, that is, by cells that express high levels of CD122 (IL-2Rβ), the receptor for both IL-2 and IL-15. Naive T cells express much lower levels of CD122 and, in the presence of proliferating CD122^{hi} cells, the injected cytokines are rapidly consumed and are only poorly stimulatory for naive T cells. This problem of cytokine consumption can be avoided by eliminating CD122^{hi} cells, that is, by transferring purified naive T cells into irradiated (T-depleted) hosts. Under these conditions, coinjection of IL-2 or IL-15 causes marked proliferation of the donor T cells.

For IL-2, proliferation is greatly augmented when the injected IL-2 is complexed with anti-IL-2 mAb; as discussed elsewhere, IL-2 mAb association boosts the biological activity of IL-2 *in vivo* (though not *in vitro*).[37] When naive T cells are transferred to irradiated mice, repeated injection of IL-2/IL-2 mAb complexes induces the donor T cells to proliferate rapidly and undergo massive expansion (Figure 1);[35,36] such proliferation applies to polyclonal T cells (Figure 1a) as well as to certain TCR transgenic lines, for example, 2C (Figure 1b). Proliferation is skewed to CD8$^+$ T cells and results in the generation of effector cells expressing high levels of granzyme B and IFN-γ. Proliferation of CD4$^+$ cells is much lower, which correlates with CD122 expression being low but significant on naive CD8$^+$ cells but almost undetectable on naive CD4$^+$ cells.[38] Similar findings apply with injection of IL-15, though, here, IL-15 activity is boosted by association with a soluble recombinant form of the IL-15 receptor α-chain.[39,40] These data on IL-2 and IL-15 refer to exposing naive T cells to cytokines after transfer to T-depleted normal mice as hosts. Similar intense proliferation occurs when naive T cells are transferred to certain strains of mice that have high constitutive levels of γ_c cytokines.[35] Proliferation is especially pronounced in CD122$^{-/-}$ hosts (Figure 2), which have high serum levels of IL-2 and presumably also IL-15 (although the latter cannot be reliably measured in serum because IL-15 is normally displayed on the cell surface bound to the IL-15Rα-chain[41]). Even though CD122$^{-/-}$ mice show marked lymphoid hyperplasia and have elevations of a variety of cytokines, the proliferation of donor naive T cells in these mice is directed selectively to IL-2 plus IL-15. This is exemplified by the finding that proliferation is undetectable when donor 2C TCR transgenic T cells are crossed to a CD122$^{-/-}$ background.[35]

As for IL-7-driven proliferation, the intense proliferation of naive T cells induced by IL-2 and IL-15 is MHC dependent.[35] Thus, when naive CD8$^+$ cells are exposed to IL-2 in irradiated hosts, proliferation becomes almost undetectable when MHC$^{-/-}$ hosts are used. However,

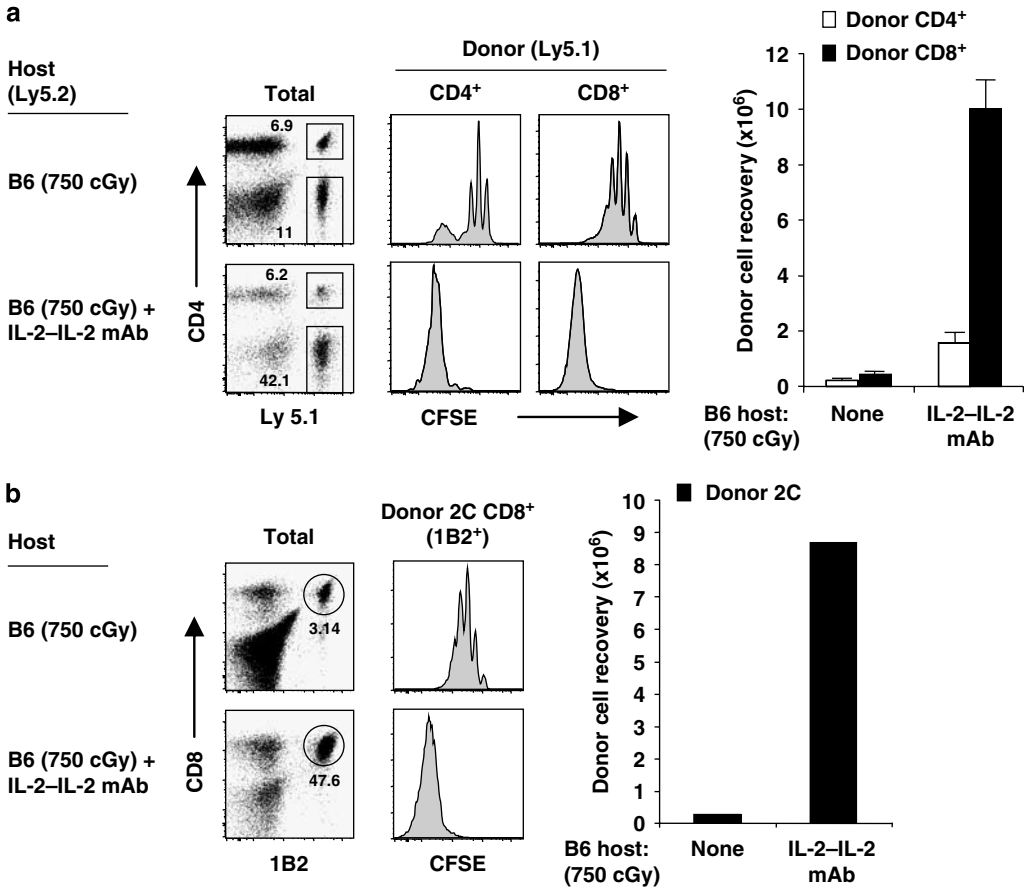

Figure 1 Proliferation of naive T cells in response to IL-2–IL-2 mAb complexes. (**a**) A mixture of fluorescence-activated cell sorting (FACS)-sorted CD44^{lo} CD4$^+$ and CD8$^+$ cells (Ly5.1) was carboxyfluorescein diacetate succinimidyl ester (CFSE) labeled and transferred into irradiated (750 cGy) B6 mice (1.5×10^6 cells of each subset per mouse). Host mice were either uninjected (top) or injected i.p. (bottom) daily for four consecutive days with IL-2–IL-2 mAb complexes. Spleen and LN cells were analyzed 1 day later (on day 5) by flow cytometry. Shown are Ly5.1 versus CD4 profiles (left) of total lymphocytes, CFSE profiles (middle) of gated donor CD4$^+$ (Ly5.1$^+$ CD4$^+$; left) and CD8$^+$ (Ly5.1$^+$ CD4$^-$; right) cells, and total donor cell recoveries from the indicated hosts (bar graph; mean ± s.d. of three mice per group). (**b**) 1–1.5×10^6 MACS-purified CFSE-labeled CD44^{lo} 2C CD8$^+$ cells (1B2$^+$) were transferred into irradiated (750 cGy) B6 mice. Host mice were either untreated (top) or treated (bottom) with IL-2–IL-2 mAb complexes as in (**a**). Spleen and LN cells were analyzed on day 5 by flow cytometry. Shown are 1B2 versus CD8 profiles (left) of total lymphocytes, CFSE profiles (middle) of gated donor 2C (1B2$^+$ CD8$^+$) cells and total donor cell recoveries from the indicated hosts (bar graph; one representative of at least three independent experiments). Numbers in the dot plots indicate percentages of cells in the gates (From reference[35]).

this finding only applies when small numbers of T cells are injected (Figure 3). With larger cell numbers, for example, 2×10^6, significant proliferation occurs, apparently because of TCR/MHC interaction occurring via T–T interaction.[35]

Despite the marked difference in the tempo of cell division, proliferation of naive T cells elicited by IL-7 versus IL-2/15 is quite similar. Thus, for each cytokine, proliferation preferentially affects CD8$^+$ cells and is MHC dependent. Likewise, at least for B7-CD28 interaction, IL-2/15-driven proliferation resembles IL-7-driven proliferation in being costimulation independent.[35] Hence, both forms of proliferation would seem to fall into the category of 'homeostatic' proliferation, the greater intensity of the response to IL-2 and IL-15 reflecting that these cytokines are much more overtly stimulatory than IL-7. It is worth mentioning that, although IL-7-mediated proliferation in T-depleted hosts has been termed lymphopenia-driven proliferation, this term is clearly inappropriate for IL-2/15-driven proliferation. Thus, as discussed earlier, the latter can occur in CD122$^{-/-}$ mice, that is, mice with marked hypertrophy of the lymphoid organs.

MEMORY T CELLS

As mentioned earlier, MP T cells are a minor subset in young life but become a dominant population in advanced age. With regard to the origin of MP cells, it is well documented that naive T cells generate large numbers of activated T cells and early memory cells following contact with specific antigen. Most of these cells are destroyed following elimination of the infectious agent concerned but a small proportion survives to become long-lived memory T cells.[5,22,42,43] In phenotype and function, these cells closely resemble the naturally-occurring subset of MP T cells. Because of this similarity, it is tacitly assumed that MP cells are the progeny of naive T cells responding to a variety of environmental antigens. It is striking, however, that at least in young adult mice the proportion of MP T cells is as high in germ-free mice, and even antigen-free mice, as in normal mice housed in a conventional environment.[33,44,45] The implication therefore is that many, perhaps most MP cells are the progeny of cells responding to self rather than foreign antigens.

In young mice, MP cells may arise largely via IL-7-mediated lymphopenia-induced proliferation. Thus, lymphopenia is marked

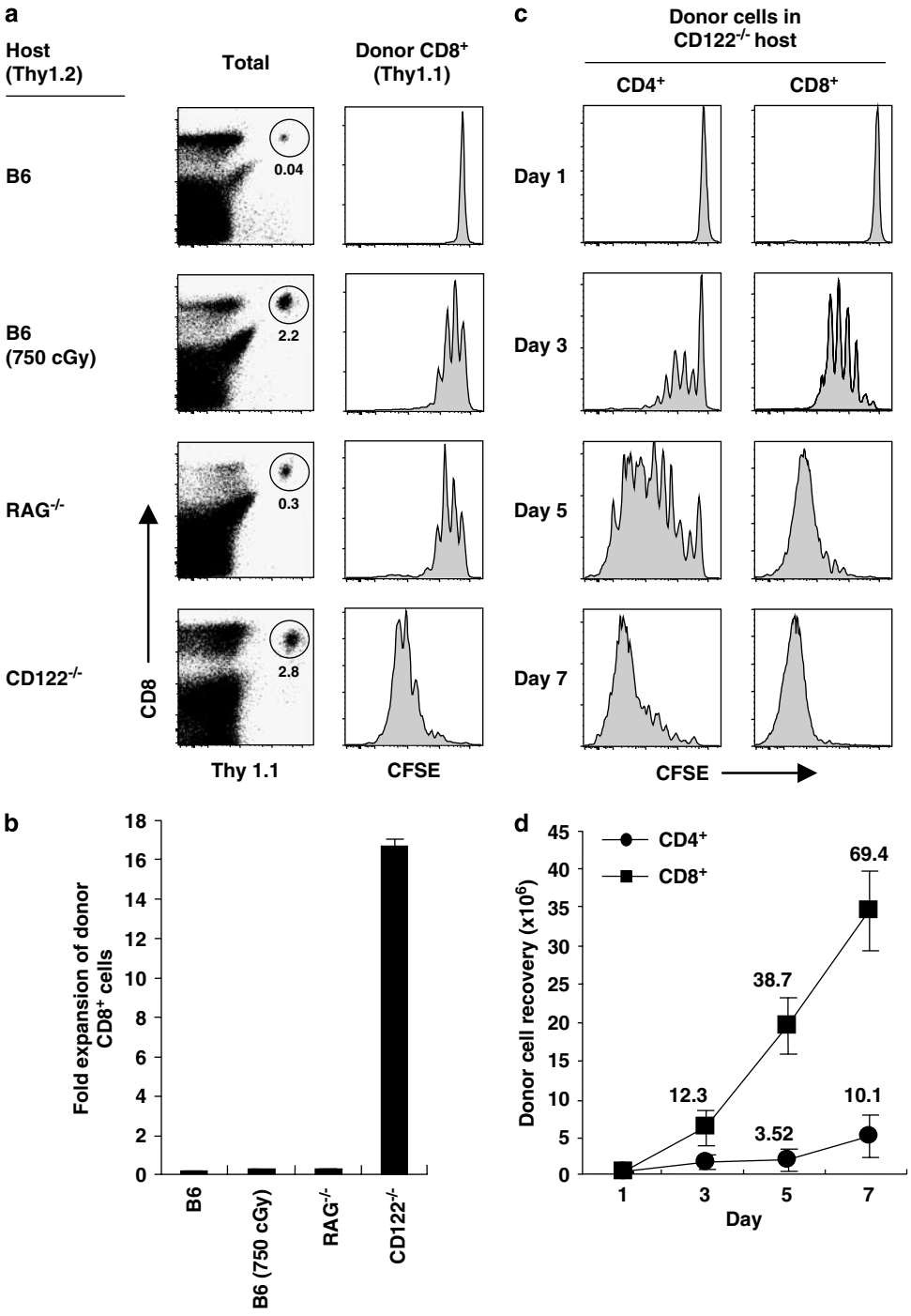

Figure 2 Proliferation of normal T cells in CD122$^{-/-}$ hosts. (**a**) Fluorescence-activated cell sorting (FACS)-sorted naive (CD44^{lo}) CD8$^+$ T cells (Thy1.1) were carboxyfluorescein diacetate succinimidyl ester (CFSE) labeled and transferred i.v. at 10^6 cells per mouse into normal B6, irradiated (750 cGy) B6, RAG$^{-/-}$ and CD122$^{-/-}$ mice. Spleen and LN cells were analyzed 4 days later by flow cytometry after staining for Thy1.1 and CD8 (left). Numbers in the dot plot indicate percentages of donor CD8$^+$ (Thy1.1$^+$ CD8$^+$) cells within the total lymphocyte populations. CFSE profiles show the proliferation of gated donor CD8$^+$ cells from the indicated hosts (right). (**b**) Fold expansion of donor cells recovered from pooled spleen and LN of mice in (**a**) (mean ± s.d. of two mice per group). (**c**) A mixture of FACS-sorted CD44^{lo} CD4$^+$ and CD8$^+$ cells (Thy1.1) was CFSE labeled and transferred into CD122$^{-/-}$ mice (0.5×10^6 cells of each population per mouse). At the indicated time points, spleen and LN cells were analyzed by flow cytometry. Shown are CFSE profiles of gated donor CD4$^+$ (Thy1.1$^+$ CD8$^-$) and CD8$^+$ (Thy1.1$^+$ CD8$^+$) cells. (**d**) Total donor cell recoveries from mice in (**c**) (mean ± s.d. of two to three mice at each time point). Numbers indicate fold expansion of donor cells at each time point (From reference[35]).

during the first 1–2 weeks of birth, that is, when T cells are first being released from the thymus. During this period the proportion of MP cells can be as high as 50%.[46] Thereafter, the proportion of these cells falls, paralleling rapid formation of the naive T cell pool. It is quite likely therefore that most of the MP T cells found in young adult life are the descendants of the initial cohort of naive thymic emigrants that entered the lymphopenic post-thymic environment soon after birth and then converted to MP cells through contact with high levels of

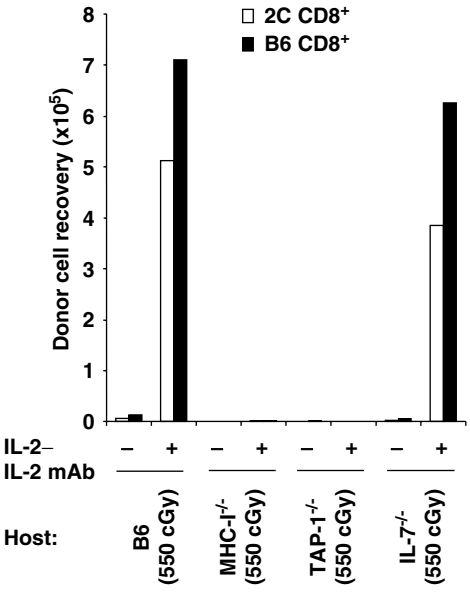

Figure 3 Major histocompatibility complex (MHC)-I requirement for IL-2–IL-2 mAb-driven proliferation. A mixture of fluorescence-activated cell sorting (FACS)-sorted CD44^{lo} B6 (Ly5.1) and 2C CD8$^+$ cells (Thy1.1) were transferred into various irradiated (550 cGy) B6, MHC-I$^{-/-}$, TAP-1$^{-/-}$ and IL-7$^{-/-}$ mice (10^5 cells of each population per mouse), followed either by no treatment or injection of IL-2–IL-2 mAb complexes. Spleen and LN cells were analyzed on day 7 by flow cytometry. Shown are total recoveries of donor B6 (Ly5.1$^+$ Thy1.1$^-$) and 2C (Ly5.1$^-$ Thy1.1$^+$) CD8$^+$ cells from the indicated hosts (From reference[35]).

IL-7. The results of following the fate of naive T cells transferred to neonatal mice are consistent with this notion, though the influence of IL-7 is less clear for CD4$^+$ cells than for CD8$^+$ cells.[47–49]

The origin of the large numbers of MP cells generated in old age is uncertain. Here, an important question is whether the gradual transition of naive to MP cells with age occurs in a germ-free environment. Direct information on this issue is limited, especially for C57BL/6 mice (the main strain used for studies on T cell homeostasis). Although some MP cells generated in aged mice kept in a conventional environment are presumably derived from responses to environmental antigens, other MP cells could arise via homeostatic mechanisms. Lymphopenia is rare in adults, which makes it unlikely that MP cells in old age are generated via an IL-7-driven homeostatic process. However, other forms of cytokine-driven homeostasis are possible. Thus, bearing in mind the intense proliferation of naive T cells induced by high levels of IL-2 and IL-15 in young adult mice (see paragraph Naive T Cells), it is conceivable that transient increases in these cytokines during intercurrent infections could cause a gradual 'bystander' switch of naive to MP cells in later life.[35] Direct evidence on this important issue is lacking.

Typical antigen-specific memory T cells consist largely of resting CD44^{hi} cells.[5,22,43] These cells resemble naive CD44^{lo} cells in expressing a CD62L^{hi} CCR7^{hi} phenotype, thus allowing the cells to recirculate through LN as well as spleen. However, a proportion of memory T cells resemble partially-activated effector cells in expressing a CD62L^{lo} CCR7^{lo} phenotype. The interrelationship of these two subsets of memory T cells is still unclear, although the high proportion of CD62L^{lo} CCR7^{lo} cells found in chronic infections suggests that cells with this phenotype are subject to repeated stimulation by specific antigen or other stimuli.[50–52] Recent work has shown that a comparable population of semi-activated T cells accounts for about 30% of MP T cells in normal unimmunized mice.[53,54] For CD8$^+$ cells, these cells have not been typed for CCR7 expression but are mostly CD62L^{lo} CD69^{hi} CD43^{hi} CD127^{lo} and have a rapid turnover *in vivo*.[53] Significantly, this subset of MP CD8$^+$ cells ceases to proliferate and disappears rapidly following transfer to MHC I$^{-/-}$ hosts, suggesting that these cells are normally maintained by continuous TCR contact with MHC I ligands, presumably self ligands. The cells probably do not require contact with γ_c cytokines because the expression of surface receptors for these cytokines, for example, CD122 (IL-2Rβ) for IL-2 and IL-15 and CD127 for IL-7, is quite low. These data apply only to the semi-activated subset of MP CD8$^+$ cells. Thus, typical resting MP CD8$^+$ cells survive well in MHC I$^{-/-}$ hosts,[53] indicating that this subset of MP CD8$^+$ cells do not require TCR/MHC interaction for cell survival. Likewise, typical resting antigen-specific memory CD8$^+$ cells generated during viral infections survive long-term after transfer to MHC I$^{-/-}$ hosts.[55]

As for CD8$^+$ cells, MP CD4$^+$ cells comprise a mixture of MHC-dependent and MHC-independent cells.[54] For CD4$^+$ cells, it has long been known that many MP cells have a relatively rapid rate of turnover *in vivo*.[5] Curiously, the turnover of MP CD4$^+$ cells remains high after transfer to hosts lacking MHC II Aβ,[54,56] implying that proliferation of the cells is MHC II independent. However, it is now clear that, despite their lack of CD4$^+$ T cells, MHC II Aβ$^{-/-}$ mice can express functional heterodimers of Aα-Eβ;[56] these heterodimers are absent in combined Aα$^{-/-}$ Eβ$^{-/-}$ (MHC II$^{\Delta/\Delta}$) mice. The significant finding is that the high background turnover rate of most (but not all) (see next paragraph) MP CD4$^+$ cells on adoptive transfer is not seen in MHC II$^{\Delta/\Delta}$ hosts, indicating that proliferation of these cells is indeed MHC II dependent.[12,54,56]

As indicated above, both for CD8$^+$ and CD4$^+$ cells a small fraction of MP T cells is engaged in chronic TCR responses to MHC ligands and displays a semi-activated phenotype. Nevertheless, a sizeable proportion of MP T cells survive for prolonged periods in MHC-deficient hosts. These latter MHC-independent MP cells display a resting CD62L^{hi} CCR7^{hi} phenotype and have a relatively slow turnover (although clearly faster than that of naive T cells). Comparable properties are shared by typical antigen-specific central memory cells. As discussed below, the survival and intermittent turnover of these resting memory T and MP T cells reflects contact with γ_c cytokines, especially IL-7 and IL-15.

For CD8$^+$ cells, normal homeostasis of resting MP cells is controlled largely by IL-15. The first evidence on this issue came from the finding that the few MP CD8$^+$ cells generated in IL-15$^{-/-}$ mice consist almost entirely of semi-activated cells with a CD122^{lo} phenotype, that is, by cells that lack receptors for IL-15 (and IL-2).[57] CD122^{hi} MP CD8$^+$ cells are conspicuously absent in IL-15$^{-/-}$ mice and are also selectively depleted in IL-15Rα$^{-/-}$ mice;[58,59] because IL-15Rα is essential for the presentation of endogenous IL-15 *in vivo*, IL-15Rα$^{-/-}$ mice fail to express IL-15 on the cell surface and thus closely resemble IL-15$^{-/-}$ mice.[41,60] These data with IL-15- and IL-15Rα-deficient mice show that the survival and turnover of resting MP CD8$^+$ cells are crucially dependent on IL-15. This requirement correlates with their high expression of CD122.

Whether resting MP CD8$^+$ cells are also dependent on IL-7 is controversial. Here, the main problem is that IL-7$^{-/-}$ mice are severely lymphopenic (reflecting the need for IL-7 for thymopoiesis) and hence are difficult to use for studying normal T cell homeostasis. Nevertheless, approaches that selectively disrupt IL-7 responsiveness after thymic development suggest that resting MP CD8$^+$ cells do require

contact with IL-7 as well as IL-15 for their survival.[61] These findings apply to nonlymphopenic hosts where the background levels of IL-7 and IL-15 are quite low. Interestingly, IL-7 transgenic mice have very large numbers of resting MP CD8$^+$ cells even on an IL-15$^{-/-}$ background, indicating that the requirement for IL-15 can be overcome by raising the level of IL-7 to a high level.[62] These data apply to cell survival. For proliferation, by contrast, IL-15 seems to be much more important than IL-7, although both cytokines contribute to the rapid homeostatic proliferation seen when MP CD8$^+$ cells are transferred to lymphopenic hosts.[63]

For MP CD4$^+$ T cells, a number of approaches have shown that many of these cells are strongly dependent on IL-7 for their survival.[54,64–66] IL-15 seems to play a lesser role than IL-7 for survival because MP CD4$^+$ cells are not reduced in IL-15$^{-/-}$ hosts.[67] Moreover, the expression of CD122 is appreciably lower on MP CD4$^+$ cells than MP CD8$^+$ cells.[38] However, examining the cytokine requirements of resting MP CD4$^+$ cells is difficult because these cells are hard to separate from the major subset of semi-activated MHC II-dependent cells which are independent of both IL-15 and IL-7.[54] This problem can be avoided by studying antigen-specific memory CD4$^+$ cells. Thus, unlike MP CD4$^+$ cells, antigen-specific memory CD4$^+$ cells consist almost entirely of resting MHC II-independent cells and are therefore an ideal population for studying the requirements for cytokines.[54] The notable finding with these resting antigen-specific memory CD4$^+$ cells is that the cells proliferate poorly and gradually disappear following transfer to IL-15$^{-/-}$ hosts, indicating prominent dependency on IL-15.[54] It is of interest that proliferation of these cells is also reduced in IL-7$^{-/-}$ hosts, implying that responsiveness of the donor cells to IL-15 is relatively poor, consistent with their low expression of CD122. On this point, resting memory CD4$^+$ cells show no reduction in their background proliferation when these cells are transferred to IL-7$^{-/-}$ hosts selectively depleted of CD122^{hi} CD8$^+$ cells and NK cells by mAb injection.[54] Hence, reflecting their low level of CD122, the partial dependency of memory CD4$^+$ cells on IL-15 becomes much more apparent when the cells do not have to compete with high-affinity cells (CD122^{hi} cells) for access to this cytokine.

Collectively, the above data indicate that, both for CD8$^+$ and CD4$^+$ cells, resting memory T cells require joint contact with IL-7 and IL-15 for their survival and occasional cell division. At least at their normal physiological concentrations, other γ_c cytokines do not seem to be involved. For IL-2, this finding may seem surprising because MP CD8$^+$ cells are CD122^{hi} and therefore responsive to IL-2. Moreover, other cells, notably CD4$^+$ CD25$^+$ T regulatory cells (T_{regs}) are strongly dependent on IL-2. The explanation for this paradox is that, unlike T_{regs}, MP CD8$^+$ cells lack the IL-2Rα chain (CD25) and therefore have much lower affinity for IL-2 than T_{regs}. Hence, the background concentration of IL-2 *in vivo* is too low to influence MP CD8$^+$ cells. However, MP CD8$^+$ cells are clearly reactive to higher concentrations of IL-2 because strong proliferation of these cells occurs following injection of exogenous IL-2, especially with injection of IL-2/IL-2 mAb complexes.[37] It is worth noting that injection of anti-IL-2 mAb alone causes appreciable proliferation of MP CD8$^+$ cells in normal mice[68] and also induces *de novo* generation of CD122^{hi} MP CD8$^+$ cells in IL-15$^{-/-}$ mice.[69] These odd findings are now known to reflect that, by forming complexes, IL-2 mAb injection boosts the biological activity of endogenous IL-2 *in vivo*.[37] With regard to other cytokines, IL-4 and IL-21 are not involved in normal T cell homeostasis but are strongly stimulatory for MP CD8$^+$ cells in above-normal concentrations.[37,70,71] For IL-4, it is of interest that the strong proliferation of MP CD8$^+$ cells induced by injection of α-galactosylceramide is mediated by IL-4 released from NKT cells.[70]

CONCLUDING COMMENTS

To summarize the above findings, most mature T cells are long-lived cells that are maintained through continuous contact with exogenous ligands, notably self MHC molecules and certain γ_c cytokines. After leaving the thymus as naive cells, mature T cells can survive for prolonged periods as typical recirculating resting cells but then gradually switch to memory and MP cells. For the latter, many MP cells could be derived via contact with self antigens but direct evidence on this issue is limited, especially for the large cohort of MP cells found in old age. In young adult animals, the presence of MP cells in germ-free animals suggests that most of these cells are the progeny of naive cells responding to self antigens plus increased levels of γ_c cytokines, especially IL-7 in the neonatal period. Based on studies with lymphopenic mice, the responding T cells proliferate briefly and then switch to resting long-lived CD44^{hi} MP cells; these cells are MHC independent and are kept alive and induced to divide intermittently via their heightened sensitivity to γ_c cytokines, especially IL-15. Precisely how this pattern of differentiation from naive to MP cells is controlled, however, is still largely obscure.

Based on studies with TCR transgenic mice, the transition of naive cells to MP cells may be skewed to T cells with above-average TCR affinity for self MHC ligands.[30,72] The fact that this transition is slow and seems to affect only a small proportion of T cells in young life presumably reflects a combination of post-thymic 'tuning' of TCR responsiveness together with only limited exposure to cytokines and low expression of certain cytokine receptors, especially CD122, on naive T cells. This tuning process is well illustrated by the relative responsiveness of CD8$^+$ cells to IL-15. As mentioned earlier, unlike MP CD8$^+$cells, naive CD44^{lo} CD8$^+$ cells are poorly responsive to physiological concentrations of IL-15 and IL-2 because of low expression of CD122, yet proliferate vigorously when exposed to high concentrations of these cytokines. Similarly, at least for IL-15, proliferation of naive CD8$^+$ cells can be induced by increasing the sensitivity of signalling via CD122, that is, by eliminating expression of SOCS-1.[73–75] Thus, for SOCS-1$^{-/-}$ mice, naive CD8$^+$ cells proliferate and switch to a memory phenotype spontaneously soon after leaving the thymus; similarly, naive SOCS-1$^{-/-}$ CD8$^+$ cells proliferate after transfer to nonlymphopenic normal mice but not IL-15$^{-/-}$ mice, implying that the cells have increased reactivity to physiological concentrations of IL-15. As with exposure of normal naive CD8$^+$ cells to exogenous IL-15 (and IL-2) (see Naive T Cells), the response of SOCS-1$^{-/-}$ naive CD8$^+$ cells to endogenous IL-15 is MHC I dependent.[74]

Paradoxically, the marked switch of naive cells to MP cells seen in SOCS-1$^{-/-}$ mice and after exposure of normal T cells to high levels of IL-2 or IL-15 is also conspicuous in IL-2$^{-/-}$, CD122$^{-/-}$ and CD25$^{-/-}$ mice.[76–78] The T cell hyperplasia in these latter three strains correlates with a paucity of IL-2-dependent CD4$^+$ CD25$^+$ Foxp3$^+$ T_{regs},[79–81] which suggests that the naive→MP cell switch in normal hosts could be somehow controlled by the presence of T_{regs}. Assessing this issue is clearly difficult because, despite intensive investigation, the mechanism of inhibition by T_{regs} is still largely obscure.

The immediate descendents of naive T cells switching to MP cells are presumably the small subset of semi-activated, MHC-dependent MP cells. Though not overtly activated, these cells have some of the features of antigen-specific effector cells and seem to differentiate rapidly into resting MP cells.[53] However, here again, the factors controlling the differentiation of proliferating MHC-dependent MP cells to resting MHC-independent cells is poorly understood. In particular, it is unclear whether this transition is similar to the generation of antigen-specific memory cells, that is, where production

of small numbers of resting memory cells is preceded by massive death of effector precursor cells. In this latter situation, the cause of wide-scale effector cell death is still controversial but may be a consequence of strong expression of T-bet induced by exposure to inflammatory cytokines such as IL-12 during priming with antigen.[82–87] Thus, limiting the induction of T-bet during priming impairs effector cell generation and promotes the production of resting central memory cells. Since levels of inflammatory cytokines are normally quite low, this latter scenario could well apply to the generation of MP T cells, although direct evidence on this issue is lacking.

Another puzzling feature of the production of MP cells is why and how these cells lose their MHC dependency. Thus, are the cells retuned to be slightly less sensitive to TCR signals or do the cells simply ignore MHC ligands because of increased sensitivity to cytokines? Assessing those and other possibilities will require further investigation.

At least in the case of $CD8^+$ cells, the dependency of MP cells on IL-15 and IL-7 reflects strong upregulation of CD122 plus maintenance of high CD127 (IL-7Rα) expression (relative to naive $CD8^+$ cells). For IL-15, upregulation of CD122 requires expression of both T-bet and the related transcription factor, EOMES;[83] expression of these two factors is very low in naive T cells but high in $CD122^{hi}$ $CD8^+$ cells. Significantly, mice with joint deficiency of T-bet and EOMES are selectively depleted of $CD122^{hi}$ $CD8^+$ cells and thus show a very similar phenotype to IL-$15^{-/-}$ mice.[83]

As for other T cell subsets, the production of MP T cells is under strict homeostatic control. Numbers of MP T cells do increase in later life but this increase is very gradual and prominent only in old age. A point to emphasize is that MP T cells have quite a rapid rate of background proliferation (relative to naive T cells), which implies that proliferation of these cells has to be balanced by a substantial amount of cell death: on average for each division, one daughter cell lives and the other dies. How such cell fate decision making is determined is obscure, although the recent evidence for asymmetric cell division could provide a clue.[88] Thus, when MP $CD8^+$ cells respond via CD122 to IL-15 bound to IL-15Rα on other cells, expression of CD122 after cell division might conceivably be confined to only one daughter cell, leaving the other cell to die via 'cytokine neglect'. The alternative possibility is that cell death is a stochastic process and is a reflection of competition for limited quantities of IL-15.

The strong dependency of T cells on IL-7 and IL-15 raises the issue of how these cytokines exert their protective effects. Recent studies suggest that, at least for $CD4^+$ cells, γ_c cytokines act largely by maintaining high expression of Bcl-2 and other anti-apoptotic molecules.[89,90]

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