Published in final edited form as:
Nat Immunol. 2011 June ; 12(6): 478–484.

Normal T cell homeostasis: the conversion of naïve cells into memory-phenotype cells

Jonathan Sprent[1] and **Charles D Surh**[2]

Jonathan Sprent: j.sprent@garvan.org.au; Charles D Surh: csurh@scripps.edu

[1]Garvan Institute of Medical Research, Sydney, New South Wales, Australia. & WCU Program, Division of Intergrative Biosciences and Biotechnology, Pohang University of Science and Technology, Pohang, Korea

[2]Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, California, USA. & WCU Program, Division of Intergrative Biosciences and Biotechnology, Pohang University of Science and Technology, Pohang, Korea

Abstract

Covert TCR signals from contact with self-ligands synergize with IL-7-induced anti-apoptotic signals to promote survival of naïve T cells in a resting state. The level of background TCR signaling in naïve T cells is set by post-thymic TCR tuning and operates at an intensity just below that required to induce entry into cell-cycle. Co-stimulation from raised levels of IL-7 and other γc cytokines can induce T cells to undergo "homeostatic" proliferation and conversion into cells with the phenotype of memory cells; many of these memory-phenotype (MP) cells may be the progeny of cells responding to self-antigens. The molecular mechanisms that control TCR/γc cytokine-driven conversion of naïve resting T cells into MP cells in normal animals are beginning to be understood.

Introduction

The pool of mature αβTCR$^+$ T cells in the secondary lymphoid organs arises through slow release of young cells from the thymus [1, 2]; formation of the T cell pool occurs largely in young life but continues into old age. T cell differentiation in the thymus involves a stringent process of selection where immature CD4$^+$8$^+$ "double-positive" (DP) T cells are screened for TCR reactivity to self peptides bound to MHC molecules [3]. Cells with high avidity for these ligands are deleted (negative selection) whereas cells with low but significant affinity receive a weak TCR signal which induces the DP cells to survive and differentiate into mature CD4$^+$8$^-$ and CD4$^-$8$^+$ single-positive (SP) T cells through contact with MHC II and MHC I molecules, respectively (positive selection). Most DP cells (around 98%) have negligible affinity for the MHC/peptides in the thymus, and these cells die rapidly in situ from "neglect" (lack of a TCR signal).

Mature CD4 and CD8 cells in the extrathymic environment are long-lived cells which can remain in interphase for many weeks or months [4, 5]. Especially in young life, typical mature resting T cells display a naïve phenotype characterized by expression of low (lo) levels of CD44 and high (hi) levels of the lymph node homing receptors, CD62L and CCR7. These cells are kept alive by TCR contact with self-peptide/MHC (pMHC) ligands plus exposure to IL-7 [1, 2]. When naïve T cells react to antigen during the immune response, a small proportion of the responding cells survives to form antigen-specific memory T cells [6]; these cells are typically CD44^{hi}, with some of the cells being CD62L^{hi} CCR7^{hi} (central memory T cells) and others being CD62L^{lo}CCR7^{lo} (effector memory T cells). Interestingly, small numbers of T cells with these markers are found in normal unimmunized animals. Such

memory-phenotype (MP) T cells account for 10–20% of T cells in young mice but increase to high levels in old age.

This article reviews recent work on the factors controlling the survival of naïve T cells and how some of these cells are induced to switch to MP cells. Before considering naïve T cell homeostasis, it is first important to discuss the evidence that most MP T cells probably arise largely through contact with self-antigens. We then discuss the survival of naïve T cells, followed by the differentiation of these cells into MP T cells.

The origin of MP cells

Since MP T cells closely resemble antigen-specific memory T cells, it has tacitly been assumed that MP cells are the progeny of cells responding to various environmental antigens. However, this simple idea is challenged by the finding that MP cells are found before birth in humans [7, 8] and in mice held under germ-free, and even antigen-free, conditions [9–11]. What then is the origin of MP cells? As discussed below, there is increasing evidence that most of these cells are the progeny of cells responding to self-antigens.

It is now well documented that typical MP T cells arise in large numbers when naïve T cells are transferred to lymphopenic hosts [1, 2, 12]. The extensive “homeostatic” proliferation (HP) of naïve T cells in lymphopenic hosts applies to both polyclonal and TCR transgenic (Tg) cells and is directed to various self-p/MHC complexes, this “anti-self” response being boosted by the raised levels of IL-7 present in lymphopenic hosts [1, 2, 13, 14]. Since the MP cells generated in lymphopenic conditions closely resemble the MP cells found in normal mice, it has been suggested that most naturally-occurring MP cells arise from low-level HP directed to self-ligands [2, 4, 15]. Strong support for this idea has come from recent studies on the antigen-specificity of MP T cells [16, 17]. Using specific p/MHC-I tetramers to detect reactive $CD8^+$ T cells, these workers found that, contrary to a previous study [18], 10–30% of antigen-specific T cells in normal unimmunized mice had a $CD44^{hi}$ phenotype. This finding is unlikely to reflect cross-reactive responses to environmental antigens because the data applied to several different peptides and to germ-free mice [16]. Also, the data are consistent with the observation that $CD44^{hi}$ $CD8^+$ T cells account for a significant proportion of the T cells found in a number of unmanipulated TCR Tg lines, including mice on a $RAG^{-/-}$ background [16]. Most of the tetramer-binding $CD44^{hi}$ MP T cells had the typical phenotype of resting central memory cells, but differed from these cells in expressing only low-levels of CD49d (α4-integrin). Since the bulk of $CD44^{hi}$ $CD8^+$ T cells in normal mice are $CD49d^{lo}$ cells, the authors concluded that most naturally-occurring MP cells arise from cells undergoing HP to self-ligands [16].

It is important to emphasize that the data implicating self-antigens as the stimulus for MP cell generation rely heavily on studies with $CD8^+$ T cells. $CD4^+$ T cells are less sensitive to HP than $CD8^+$ T cells [1, 14, 19], and the origin of MP $CD4^+$ T cells may be more complex. Thus, nearly all of the specific peptide-binding $CD4^+$ T cells in unimmunized mice were found to be typical naïve $CD44^{lo}$ cells [20].

For $CD8^+$ T cells, is notable that the antigen-specific MP cells found in normal mice differ from naïve cells in giving rapid proliferative responses to antigen and strong production of IFN-γ in response to inflammatory cytokines [16]. Hence, MP cells may play a vital role in the early stages of the immune response to pathogens, both for innate and adaptive responses. This function could be especially important when efficient immune responses are essential, i.e. in the neonatal period and old age. In this respect, it is of interest that MP cells are prominent in both of these stages, MP production in neonatal mice reflecting T-lymphopenia in young life.

TCR tuning and the maintenance of naïve T cells

Although the physiological purpose of positive selection has long been debated, it is now thought that selecting T cells for weak but significant reactivity to self peptides in the thymus allows the cells to engage in continuous low-level TCR interaction with these same or cross-reactive peptides in the periphery [1, 4, 21]. Such interaction provides naïve T cells with tonic TCR signals which, in conjunction with IL-7, maintain cell viability by promoting expression of pro-survival molecules such as Bcl-2. Since naïve T cells are resting cells, the intensity of tonic TCR signaling is presumed to be below the threshold needed to induce overt activation. Here, it is notable that positive selection of DP cells in the thymus is association with upregulation of CD69, an activation marker, whereas mature extrathymic T cells do not express this marker unless activated with antigen [3]. Also, DP cells are more sensitive to activation by antigen than mature T cells [3, 22], which correlates with DP cells having higher expression of miR-181a, a phosphatase regulator [23].

These and other findings indicate that, after positive selection, T cells undergo a process of TCR desensitization before entering the secondary lymphoid tissues [24, 25]. Such TCR tuning modulates the intensity of TCR signaling and is thought to be especially important for cells with relatively high self reactivity. For these T cells, TCR tuning reduces TCR signaling to just below the level required for entry into cell-cycle, thereby keeping the cells in a quiescent, self-tolerant state. Such cells are highly sensitive to proliferation in lymphopenic hosts, which may account for why lymphopenia predisposes to the development of autoimmune disease; thus, HP directed to ubiquitous weak self-peptides may activate autoaggressive T cells with cross-reactive specificity for sequestered antigens, i.e. the targets for autoimmune disease [4]. High sensitivity to HP applies to a number of TCR TG lines, but is low or undetectable for other lines, notably the HY $CD8^+$ line [26, 27]. These lines are considered to have below-average affinity for self-ligands.

TCR tuning occurs at a late stage of positive selection and, at least for $CD4^+$ T cells, reflects interaction with MHC ligands expressed in the thymic medulla, either on epithelial cells or dendritic cells [28]. For high-affinity T cells, TCR tuning involves upregulation of molecules that limit TCR responsiveness, notably the adaptor Cbl-b which blocks Vav activation [29–31], SHP-1 phosphatase [28], and CD5 which is constitutively associated with SHP-1 [32, 33]. TCR tuning by CD5 has elicted particular interest because surface CD5 levels correlate directly with the intensity of HP. Thus, $CD8^+$ TCR Tg lines with high sensitivity to HP in lymphopenic hosts, e.g. OT-I and 2C, have a $CD5^{hi}$ phenotype, whereas cells from lines that fail to undergo HP, e.g. HY, are $CD5^{lo}$ cells [27]. Likewise, purified subsets of polyclonal $CD5^{hi}$ cells from normal mice show stronger HP responses than $CD5^{lo}$ cells [19]. In addition to upregulating negative regulators, TCR tuning is associated with altered expression of various cell-surface molecules with costimulatory function, including CD2 [34] and CD8, which enhances TCR/MHC I interaction [35–37].

Maintaining naïve T cells in a quiescent state is a complex process requiring the interplay of a number of different negative regulatory mechanisms that prevent cell activation [38]. Repression of NFκB activity is especially important and involves continuous synthesis of the NFκB inhibitor, IkB, via two members of the forkhead family of transcription factors, Foxo3a and Foxj1. Expression of these factors is high in naïve T cells and their deletion causes pathology through hyperproliferation of T cells [39, 40]. T cell quiescence also depends on continuous inactivation of NFAT. Here, calcineurin-mediated NFAT dephosphorylation and translocation to the nucleus is prevented in resting T cells by the autoinhibitory domain of calcineurin [38]. Nevertheless, NFAT can also serve to maintain the resting status of T cells by repressing the cell cycle activator, Cdk4; thus, $NFATc2^{-/-}$ mice show splenomegaly and signs of T cell activation, correlating with increased levels of Cdk4 protein [41, 42]. In this

respect, T cell quiescence requires the presence of a variety of transcription factors that downregulate the expression of genes essential for cell cycle progression, e.g. Cdk2, or cause upregulation of $p27^{kip1}$, a negative regulator of the cell cycle. One such factor is Tob, which is highly expressed in naïve T cells [43] and may be maintained by a Kruppel-like transcription factor, KLF2 (LKLF). Thus, KLF2-deficient T cells show hyperproliferation and expression of activation markers [44, 45]; as discussed later, however, KLF2 deficiency can have other effects on T cells – see below. For $CD8^+$ T cells, quiescence of naïve cells also involves two other transcription factors, ELF4 and KLF4 [46]. Based on studies with $ELF4^{-/-}$ $CD8^+$ T cells, ELF4 appears to activate KLF4 which reduces TCR sensitivity, perhaps via the cell cycle inhibitor, P21. T cell quiescence also requires negative regulation by Foxp1, as indicated by the activated phenotype of mature T cells, including SP thymocytes, after conditional deletion of Foxp1 in DP thymocytes [47]. How Foxp1 induces quiescence is still unclear.

Tonic TCR signaling of T cells is vital for maintaining cell viability. This is apparent from the finding that deletion or mutation of various molecules involved in TCR signaling can shorten the lifespan of naïve T cells in vivo. Thus, diminished survival of naïve T cells is seen in mice lacking Vav1 [48], WASP [49], the adaptor Nck [50], the RNA-binding protein, hnRNPLL [51], a Rho-Rac GTP exchange factor, Dock 8 [52], and the β3 regulatory subunit of voltage-gated calcium channels [53]. In these various situations, the reduced lifespan of naïve T cells generally correlates with TCR hyporesponsiveness.

Effects of depriving T cells of MHC contact

For normal naïve T cells, these cells can survive in interphase for prolonged periods, months in mice and years in humans [5, 54]. In the case of murine $CD8^+$ T cells, it is well accepted that depriving these cells of contact with MHC I molecules [55, 56] or ablating TCR expression [57, 58] causes naïve cells to die within several weeks. In these studies, the half-life of the cells ranged from 2–7 days for naïve cells transferred to MHC I-deficient hosts to 16–19 days following TCR ablation. For T cell transfer studies, the presence of MHC I on the transferred cells and the use of lymphopenic hosts could complicate the results. These problems were avoided in a recent study where MHC $I^{-/-}CD8^+$ T cells prepared from bone marrow chimeras were transferred to nonlymphopenic MHC $I^{-/-}$ hosts [37]. Under these conditions, the half-life of naïve CD8 cells was about 10 days.

The situation with $CD4^+$ T cells is distinctly different. Indeed, despite intensive investigation, the influence of TCR/MHC II interaction on naïve $CD4^+$ T cell survival is still unresolved. Thus, in some studies, $CD4^+$ T cells disappeared quite rapidly following transfer to MHC $II^{-/-}$ hosts [59–61], whereas in other studies naïve $CD4^+$ T cells survived as resting cells for prolonged periods [62, 63]. A complication in these latter studies, however, is that in some of the studies the hosts were lymphopenic, and therefore had raised levels of cytokines, or the hosts may have expressed residual MHC II in the form of Aα/Eβ heterodimers [64]. Following TCR ablation in situ, the half-life of naïve $CD4^+$ T cells varied from about 27 days in one study [57] to 46 days in another study [58], relative to 78 days for normal cells. As a whole, the data suggest that CD4 cells do depend on MHC contact for their survival, but probably less so than $CD8^+$ T cells. In one study, $CD4^+$ T cells parked in MHC $II^{-/-}$ hosts showed impaired cell motility and decreased ability to interact with dendritic cells (DC) [65]. It was concluded that tonic TCR signaling by self MHC II ligands maintains cell motility by promoting basal activation of Rap1 and Rac1.

Tonic TCR signaling may also be beneficial in promoting responsiveness to foreign antigens. Thus, depriving $CD4^+$ T cells of MHC II contact was found to induce a rapid decrease in TCRζ phosphorylation and reduced responses to foreign antigens [66]. Similar

findings occurred following selective ablation of DC in situ using the CD11c.DOG mouse system, both for $CD4^+$ and $CD8^+$ T cells [67].

Despite these findings, there is also evidence that loss of MHC contact can lead to partial reversal of TCR tuning and an increase in responsiveness to antigen. For TCR tuning, CD5 levels decrease following T cell transfer to MHC-deficient hosts, both for $CD8^+$ T cells [37] and $CD4^+$ T cells [58, 65, 68], thereby lessening the negative effect of CD5 on TCR signaling. Likewise, for $CD8^+$ T cells, parking these cells in MHC $I^{-/-}$ hosts leads to an increase in cell-surface expression of CD8 paralleled by a decrease in IL-7Rα expression [37]. Such reversal of TCR tuning is reported to cause $CD8^+$ T cells to display increased TCR reactivity to weak TCR agonists, though not to strong agonists. The results for $CD4^+$ T cells are less clear cut (reviewed by [2]), though in some studies depriving these cells of MHC II contact caused increased TCR responsiveness as defined by elevated Ca^{2+} responses after TCR ligation [68] and the capacity to reject syngeneic MHC II^+ skin grafts [69]. Likewise, unseparated T cells transferred to combined MHC $I^{-/-}$ $II^{-/-}$ hosts acquired the capacity to reject grafts of syngeneic normal pancreas [70]. Though consistent with reversal of TCR tuning, these findings for $CD4^+$ T cells are again complicated by the use of lymphopenic hosts and the possible presence of Aα/Eβ heteterodimers. This concern does not apply to the experiments on $CD8^+$ T cells because nonlymphopenic hosts were used for these studies.

The observation that naïve $CD8^+$ T cells parked in MHC $I^{-/-}$ hosts acquired increased reactivity to weak agonist ligands [37] is of particular interest because it sheds new light on the fundamental issue of why T cells need to undergo positive selection. Here, the original explanation was that positive selection to self components increases the capacity of T cells to respond to foreign antigens [71]. But precisely how self recognition could improve responses to foreign antigens was never clearly explained. So, interest has now switched to the notion that the prime purpose of positive selection is to guide T cell survival in the post-thymic environment [4]. However, in re-considering the original explanation, it is notable that T cell responses to foreign peptides are augmented by the presence of low-affinity nonstimulatory peptides [72–75]. Here, it is worth recalling that the initial findings on positive selection came from studies on MHC-heterozygous $(A\times B)F_1 \rightarrow$ parent BM chimeras, which showed that F_1 T cells differentiating in the thymus of parent A gave better responses to foreign antigen presented by APCs from parent A than from parent B. These findings led to the conclusion that “self” is imprinted in the thymus and that thymic and post-thymic recognition of weak self-pMHC ligands somehow enhances reactivity to foreign peptides. But, in light of the newer data on the augmenting role of nonstimulatory peptides for optimal T cell responses, one can argue that the main purpose of positive selection is to generate a repertoire of T cells that has significant TCR binding affinity for the weak MHC-associated self peptides present on normal APCs, such recognition serving to augment T/APC interaction and thereby enhance TCR contact with foreign peptides. This idea is a variation on the previous suggestion that the tonic TCR signals resulting from self recognition maintain TCR sensitivity to foreign antigen [66]. Both models are compatible with the view that self peptide recognition can have other functions, namely providing a stimulus for T cell survival [1].

Role of cytokines

By itself, tonic TCR signaling is not enough to keep naïve T cells alive. In addition, the cells have to make contact with IL-7 [1, 76]. Thus, naïve $CD4^+$ and $CD8^+$ T cells die within 1–2 weeks after transfer to IL-$7^{-/-}$ hosts [1, 76] or following conditional deletion of IL-7Rα[77]. IL-7 binding to IL-7R promotes survival by upregulating the expression of anti-apoptotic molecules, especially Bcl-2 and Mcl-1 [78]. However, IL-7 also plays an important role in maintaining normal cell metabolism because, in addition to reducing lifespan, conditional

deletion of IL-7R causes naïve T cells to decrease in size and fail to maintain a basal rate of glycolytic flux [77, 79]. IL-7 also has other effects on T cells, notably maintaining expression of CD8 and modulating expression of IL-7Rα a process termed "co-receptor tuning" [36]. IL-7 is synthesized largely by CD45-negative stromal cells and is most prominent in thymus, lymph nodes and bone marrow [80–82].

As mentioned above, IL-7 responsiveness is controlled by an autocrine loop where signaling via IL-7R limits *IL-7Rα* genetranscription [36]. However, the factors controlling responsiveness to IL-7 are highly complex and involve the interplay of a number of transcription factors. For naïve T cells, the influence of the Foxo subfamily of Forkhead transcription factors, especially Foxo1, is particularly important [83–85]. Thus, conditional deletion of Foxo1 in T cells leads to a marked decrease in expression of IL-7Rα associated with reduced levels of Bcl-2 and a paucity of naïve T cells; Foxo1 appears to maintain IL-7Rα expression by binding to the proximal *IL-7Rα* promoter. Interestingly, in addition to controlling IL-7R expression, Foxo1 maintains upregulation of several molecules involved in T cell homing, namely CD62L, CCR7 and $S1P_1$. Thus, expression of these molecules is considerably reduced in $Foxo1^{-/-}$ naïve T cells, reflecting that Foxo1 binds to the promoter for KLF2, which is known to guide CD62L and $S1P_1$ expression [86, 87]. Foxo1 control of T cell homing receptors may be crucial for directing naïve cells to the main sites of IL-7 synthesis, namely the T cell areas in lymph nodes. Further information on the control of IL-7 responsiveness has come from studies on Slfn2, a member of the Schlafen family of transcription factors [88]. Mice with *Slfn2* mutation show reduced numbers of naïve T cells, poor responsiveness to IL-7 and increased sensitivity to apoptotic signals. Although the functions of Slfn2 are still unclear, it may be relevant that the mutant cells show low expression of CD62L and IL-7Rα. Hence, like Foxo1, Slfn2 may act in part by controlling responsiveness to IL-7.

Under physiological conditions, continuous interaction of naïve T cells with cytokines seems to be limited to IL-7. For $CD8^+$ T cells, however, optimal survival of naïve cells also requires joint contact with IL-15; thus, numbers of naïve $CD8^+$ T cells (but not $CD4^+$ T cells) are mildly reduced in $IL\text{-}15^{-/-}$ mice [89]. Nevertheless, naïve cells do show responsiveness to raised levels of other γc cytokines, especially IL-2. In fact, exposing $CD8^+$ T cells to high levels of IL-2 (or IL-15) induces vigorous proliferation of naïve cells, both in vivo and in vitro [90]; proliferation of $CD4^+$ T cells is much less, which correlates with expression of CD122, the β-chain of the IL-2/IL-15 receptor, being low but significant on naïve $CD8^+$ T cells but undetectable on $CD4^+$ T cells.

With regard to IL-7, it was mentioned earlier that a notable feature of IL-7-dependent HP in lymphopenic hosts is that naïve $CD8^+$ T cells generally proliferate much more rapidly than $CD4^+$ T cells [14, 26]. Likewise, proliferation induced by injection of exogenous IL-7 (or IL-2) is more intense for $CD8^+$ T cells than $CD4^+$ T cells [91, 92]. This difference does not reflect IL-7R expression levels because both T cell subsets show the same density of IL-7R. Recently, the enhanced sensitivity of $CD8^+$ T cells to cytokines was found to correlate with cell-surface expression of lipid rafts [19]. Thus, as defined by surface GM1 staining, $CD8^+$ T cells display higher expression of lipid rafts than $CD4^+$ T cells. Lipid raft expression on $CD8^+$ T cells is induced at a late stage of positive selection and correlates directly with cytokine responsiveness and CD5 levels, cells with a $GM1^{hi}CD5^{hi}$ phenotype being more sensitive to IL-7 and other γc cytokines than $GM1^{lo}CD5^{lo}$ cells.

TCR control of cytokine responsiveness

Why naïve T cells require a combination of both TCR signaling and cytokine contact to remain alive is still unclear. For cytokines, IL-7 is presumed to function simply by

maintaining expression of Bcl-2. But how tonic TCR signals promote cell viability is a mystery. One possibility is that, instead of directly inducing expression of pro-survival molecules, the weak TCR signals resulting from interaction with self-pMHC ligands function indirectly by augmenting responsiveness to cytokines. Support for this idea has come from the finding that parking naïve $CD8^+$ T cells in an MHC I-deficient environment causes a rapid loss of sensitivity to γc cytokines, correlating with reduced expression of GM1 [19]. The implication therefore is that the main purpose of TCR tuning may be to modulate the sensitivity of mature T cells to cytokines. Assessing this idea will require further investigation.

Conversion of naïve T cells to MP cells

In the many situations where interfering with tonic TCR signaling leads to reduced numbers of naïve T cells, there is generally a reciprocal increase in numbers of MP cells. In part, the generation of these cells may reflect HP due to lymphopenia. But lymphopenia can also predispose to infection and thereby induce naïve T cells to respond to a variety of environmental antigens, thus generating antigen-specific memory cells. Here, the effects of transferring naïve T cells to lymphopenic $RAG^{-/-}$ or SCID hosts is instructive. In these hosts, most of the donor cells undergo a pattern of slow proliferation typical of IL-7-induced HP. However, a small proportion of the cells divide rapidly and soon account for the vast majority of the proliferating cells. Significantly, these fast-dividing cells are much less frequent in germ-free SCID hosts [93]. Hence, many of the activated/memory T cells generated under lymphopenic conditions may arise from cells responding to foreign antigens; this is especially likely in hosts with chronic lymphopenia, which are especially prone to infection. Nevertheless, some of the fast-dividing cells in lymphopenic hosts may be bystander naïve T cells driven by the high levels of γc cytokines released by the antigen-reactive T cells in these hosts [93]. This scenario may apply to the rapid T cell turnover seen in neonatal mice [94].

As mentioned earlier, cells with features of antigen-specific activated and resting T memory cells are found in normal immunocompetent adult mice, including germ-free and antigen-free mice. Therefore, many of these MP cells seem to be the progeny of cells responding to self-pMHC ligands. For both $CD4^+$ and $CD8^+$ T cells, around one-third of MP cells have a rapid rate of turnover and display markers of activated T cells [54, 95, 96]. These cells disappear or revert to resting cells after transfer to MHC-deficient hosts, implying that the cells are proliferating in response to MHC-associated peptides, presumably mostly self-peptides. Some of these cells survive to form resting MP cells, but many may die rapidly; this is likely because the proportion of resting MP cells remains relatively constant during young adult life.

Why a proportion of naïve T cells undergoes steady-state proliferation and differentiation into MP cells in response to self ligands in normal unimmunized animals is a matter for speculation. A likely possibility is that proliferation is initiated by transient increases in concentrations of one or more γc cytokines, e.g. IL-7, IL-2 or IL-15. This idea fits with the finding that naturally-occurring MP cells closely resemble the progeny of cells responding to IL-7 during HP or after exposure to exogenous IL-2 or IL-15. On this point, it is of interest that brief exposure of DC to mild thermal stress (culture at 41.5° C for 90 min) causes expression of cell-surface HSP70, NFκB activation and increased synthesis of IL-15 [97]. Under normal conditions, one can envisage that stringent immunoregulatory mechanisms are necessary to limit synthesis of IL-15 and other stimulatory cytokines by DC and macrophages. Here, signaling via CD24 [98] and also TAM receptors for ingestion of apoptotic cells [99] could be important because mice lacking these molecules show massive lymphadenopathy. For IL-7, increased responsiveness to this cytokine might reflect

dysregulation by a population of IL-7Rα$^+$ DC [14], although this idea is disputed [100]. For other cytokines, low levels of IL-2 are synthesized constitutively in normal mice [101] and might reach high levels in certain microenvironments, perhaps reflecting intermittent synthesis by autoaggressive T cells. For IL-4, it is notable that hyperproliferation and generation of large numbers of MP cells are a feature of KLF2$^{-/-}$ mice and also tyrosine kinase Itk$^{-/-}$ mice [102]. The MP cells in these mice are present in the thymus as well as in the periphery and arise through contact with IL-4 released from an expanded population of T cells expressing the transcription factor PLZF. Interestingly, large numbers of IL-4-producing PLZF$^+$ T cells are found in normal BALB/c mice, which resolves the paradox of why MP cells are much more conspicuous in this strain than in other mouse strains.

In addition to contact with cytokines, the switch of naïve T cells into MP cells may involve other mechanisms, e.g. transient loss of contact with the inhibitory action of T regulatory cells or subtle alterations in the intensity of tonic TCR signaling; for the latter, naïve T cells are reported to proliferate and form MP cells in a bystander manner following exposure to pathogen-activated DC, apparently reflecting increased self recognition due to enhanced costimulation [103]. A switch to MP cells might also reflect a transient loss of negative signaling in naive cells through interruption of contact between PD-1 or CTLA-4 on T cells and their respective ligands on DC [104]. Another possibility is that MP cells arise in part through generation of a new TCR via “TCR revision” following contact with self antigens [105]; on this point, it is of interest that post-revision T cells have a high rate of turnover. Despite these various possibilities, a clear understanding of the mechanisms guiding the “background” generation of MP cells will require further investigation. To avoid the problem of responses to environmental antigens, it will be important to obtained detailed information on MP cells generated under germ-free – and optimally antigen-free – conditions.

Acknowledgments

This work was supported by grants from NHMRC (Australia), NIH (USA) and KOSEF (Korea).

References

1. Surh CD, Sprent J. Homeostasis of naive and memory T cells. Immunity. 2008; 29:848–862. [PubMed: 19100699]
2. Takada K, Jameson SC. Naive T cell homeostasis: from awareness of space to a sense of place. Nat Rev Immunol. 2009; 9:823–832. [PubMed: 19935802]
3. Starr TK, Jameson SC, Hogquist KA. Positive and negative selection of T cells. Annu Rev Immunol. 2003; 21:139–176. Epub 2002 Oct 2016. [PubMed: 12414722]
4. Sprent J, Cho JH, Boyman O, Surh CD. T cell homeostasis. Immunol Cell Biol. 2008; 86:312–319. [PubMed: 18362947]
5. Sprent J, Tough DF. Lymphocyte life-span and memory. Science. 1994; 265:1395–1400. [PubMed: 8073282]
6. Cui W, Kaech SM. Generation of effector CD8+ T cells and their conversion to memory T cells. Immunol Rev. 236:151–166. [PubMed: 20636815]
7. Szabolcs P, et al. Coexistent naive phenotype and higher cycling rate of cord blood T cells as compared to adult peripheral blood. Exp Hematol. 2003; 31:708–714. [PubMed: 12901976]
8. Byrne JA, Stankovic AK, Cooper MD. A novel subpopulation of primed T cells in the human fetus. J Immunol. 1994; 152:3098–3106. [PubMed: 8144905]
9. Dobber R, Hertogh-Huijbregts A, Rozing J, Bottomly K, Nagelkerken L. The involvement of the intestinal microflora in the expansion of CD4+ T cells with a naive phenotype in the periphery. Dev Immunol. 1992; 2:141–150. [PubMed: 1386544]

10. Vos Q, Jones LA, Kruisbeek AM. Mice deprived of exogenous antigenic stimulation develop a normal repertoire of functional T cells. J Immunol. 1992; 149:1204–1210. [PubMed: 1386859]
11. Huang T, Wei B, Velazquez P, Borneman J, Braun J. Commensal microbiota alter the abundance and TCR responsiveness of splenic naive CD4+ T lymphocytes. ClinImmunol. 2005; 117:221–230.
12. Hamilton SE, Wolkers MC, Schoenberger SP, Jameson SC. The generation of protective memory-like CD8+ T cells during homeostatic proliferation requires CD4+ T cells. Nat Immunol. 2006; 7:475–481. [PubMed: 16604076]
13. Napolitano LA, et al. Increased production of IL-7 accompanies HIV-1-mediated T-cell depletion: implications for T-cell homeostasis. Nat Med. 2001; 7:73–79. [PubMed: 11135619]
14. Guimond M, et al. Interleukin 7 signaling in dendritic cells regulates the homeostatic proliferation and niche size of CD4+ T cells. Nat Immunol. 2009; 10:149–157. [PubMed: 19136960]
15. Surh CD, Boyman O, Purton JF, Sprent J. Homeostasis of memory T cells. Immunol Rev. 2006; 211:154–163. [PubMed: 16824125]
16. Haluszczak C, et al. The antigen-specific CD8+ T cell repertoire in unimmunized mice includes memory phenotype cells bearing markers of homeostatic expansion. J Exp Med. 2009; 206:435–448. Probing the relationship of naïve and MP T cells, this paper uses specific peptide-loaded MHC I tetramers to show that the unprimed repertoire of T cells for foreign peptides is much the same for naïve and memory cells, and applies to germ-free as well as normal mice. The data imply that many MP cells maybe the progeny of cells responding to self antigens. [PubMed: 19188498]
17. La Gruta NL, et al. Primary CTL response magnitude in mice is determined by the extent of naive T cell recruitment and subsequent clonal expansion. J Clin Invest. 2010; 120:1885–1894. [PubMed: 20440073]
18. Obar JJ, Khanna KM, Lefrancois L. Endogenous naive CD8+ T cell precursor frequency regulates primary and memory responses to infection. Immunity. 2008; 28:859–869. Epub 2008 May 2022. [PubMed: 18499487]
19. Cho JH, Kim HO, Surh CD, Sprent J. T cell receptor-dependent regulation of lipid rafts controls naive CD8+ T cell homeostasis. Immunity. 2010; 32:214–226. Investigatingwhy naïve $CD8^+$ T cells are more responsive than $CD4^+$ T cells to certain γc cytokines, this paper showsthat tonic TCR signaling on $CD8^+$ T cells induceshigh expression of lipid rafts, which in turn amplifies the responsiveness to IL-2 and IL-15. [PubMed: 20137986]
20. Moon JJ, et al. Naive CD4(+) T cell frequency varies for different epitopes and predicts repertoire diversity and response magnitude. Immunity. 2007; 27:203–213. Epub 2007 Aug 2016. [PubMed: 17707129]
21. Garbi N, Hammerling GJ, Probst HC, van den Broek M. Tonic T cell signalling and T cell tolerance as opposite effects of self-recognition on dendritic cells. Curr Opin Immunol. 2010; 22:601–608. [PubMed: 20880686]
22. Sebzda E, et al. Mature T cell reactivity altered by peptide agonist that induces positive selection. J Exp Med. 1996; 183:1093–1104. [PubMed: 8642251]
23. Li QJ, et al. miR-181a is an intrinsic modulator of T cell sensitivity and selection. Cell. 2007; 129:147–161. Epub 2007 Mar 2022. [PubMed: 17382377]
24. Grossman Z, Singer A. Tuning of activation thresholds explains flexibility in the selection and development of T cells in the thymus. Proc Natl Acad Sci U S A. 1996; 93:14747–14752. [PubMed: 8962126]
25. Modiano JF, Johnson LD, Bellgrau D. Negative regulators in homeostasis of naive peripheral T cells. Immunol Res. 2008; 41:137–153. [PubMed: 18415030]
26. Ernst B, Lee DS, Chang JM, Sprent J, Surh CD. The peptide ligands mediating positive selection in the thymus control T cell survival and homeostatic proliferation in the periphery. Immunity. 1999; 11:173–181. [PubMed: 10485652]
27. Kieper WC, Burghardt JT, Surh CD. A role for TCR affinity in regulating naive T cell homeostasis. J Immunol. 2004; 172:40–44. [PubMed: 14688307]
28. Stephen TL, Tikhonova A, Riberdy JM, Laufer TM. The activation threshold of CD4+ T cells is defined by TCR/peptide-MHC class II interactions in the thymic medulla. J Immunol. 2009; 183:5554–5562. [PubMed: 19843939]

29. Bachmaier K, et al. Negative regulation of lymphocyte activation and autoimmunity by the molecular adaptor Cbl-b. Nature. 2000; 403:211–216. [PubMed: 10646608]
30. Chiang YJ, et al. Cbl-b regulates the CD28 dependence of T-cell activation. Nature. 2000; 403:216–220. [PubMed: 10646609]
31. Teh CE, Daley SR, Enders A, Goodnow CC. T-cell regulation by casitas B-lineage lymphoma (Cblb) is a critical failsafe against autoimmune disease due to autoimmune regulator (Aire) deficiency. Proc Natl Acad Sci U S A. 2010; 107:14709–14714. [PubMed: 20668237]
32. Tarakhovsky A, et al. A role for CD5 in TCR-mediated signal transduction and thymocyte selection. Science. 1995; 269:535–537. [PubMed: 7542801]
33. Perez-Villar JJ, et al. CD5 negatively regulates the T-cell antigen receptor signal transduction pathway: involvement of SH2-containing phosphotyrosine phosphatase SHP-1. Mol Cell Biol. 1999; 19:2903–2912. [PubMed: 10082557]
34. Teh SJ, Killeen N, Tarakhovsky A, Littman DR, Teh HS. CD2 regulates the positive selection and function of antigen-specific CD4–CD8+ T cells. Blood. 1997; 89:1308–1318. [PubMed: 9028954]
35. Maile R, et al. Peripheral “CD8 tuning” dynamically modulates the size and responsiveness of an antigen-specific T cell pool in vivo. J Immunol. 2005; 174:619–627. [PubMed: 15634879]
36. Park JH, et al. ‘Coreceptor tuning’: cytokine signals transcriptionally tailor CD8 coreceptor expression to the self-specificity of the TCR. Nat Immunol. 2007; 8:1049–1059. [PubMed: 17873878]
37. Takada K, Jameson SC. Self-class I MHC molecules support survival of naive CD8 T cells, but depress their functional sensitivity through regulation of CD8 expression levels. J Exp Med. 2009; 206:2253–2269. Centering on the role of TCR/MHC interaction on T cell survival, this paper shows that depriving naïve CD8 cells of contact with MHC I ligands in nonlymphopenic hosts leads a shortened lifespan but upregulation of CD8 expression in the surviving cells. The cells are thereby re-tuned to give enhanced responses to foreign antigens, though only to weak antigens. [PubMed: 19752186]
38. Liu JO. The yins of T cell activation. Sci STKE. 2005; 2005:re1. [PubMed: 15632417]
39. Lin L, Spoor MS, Gerth AJ, Brody SL, Peng SL. Modulation of Th1 activation and inflammation by the NF-kappaB repressor Foxj1. Science. 2004; 303:1017–1020. [PubMed: 14963332]
40. Lin L, Hron JD, Peng SL. Regulation of NF-kappaB, Th activation, and autoinflammation by the forkhead transcription factor Foxo3a. Immunity. 2004; 21:203–213. [PubMed: 15308101]
41. Xanthoudakis S, et al. An enhanced immune response in mice lacking the transcription factor NFAT1. Science. 1996; 272:892–895. [PubMed: 8629027]
42. Baksh S, et al. NFATc2-mediated repression of cyclin-dependent kinase 4 expression. Mol Cell. 2002; 10:1071–1081. [PubMed: 12453415]
43. Tzachanis D, et al. Tob is a negative regulator of activation that is expressed in anergic and quiescent T cells. Nat Immunol. 2001; 2:1174–1182. [PubMed: 11694881]
44. Hua X, Thompson CB. Quiescent T cells: actively maintaining inactivity. Nat Immunol. 2001; 2:1097–1098. [PubMed: 11725297]
45. Buckley AF, Kuo CT, Leiden JM. Transcription factor LKLF is sufficient to program T cell quiescence via a c-Myc--dependent pathway. Nat Immunol. 2001; 2:698–704. [PubMed: 11477405]
46. Yamada T, Park CS, Mamonkin M, Lacorazza HD. Transcriptionfactor ELF4 controls the proliferation and homing of CD8+ T cells via the Kruppel-like factors KLF4 and KLF2. Nat Immunol. 2009; 10:618–626. Investigating the control of naïve T cell quiescence, this paper shows that ELF4−/− and KLF4−/− mice both developa progressive increase in numbers of MP CD8 cells. The data suggest that, in normal CD8 cells, ELF4 induces synthesis of KLF4 which serves to maintain cell-cycle arrest. [PubMed: 19412182]
47. Feng X, et al. Foxp1 is an essential transcriptional regulator for the generation of quiescent naive T cells during thymocyte development. Blood. 2010; 115:510–518. [PubMed: 19965654]
48. Fujikawa K, et al. Vav1/2/3-null mice define an essential role for Vav family proteins in lymphocyte development and activation but a differential requirement in MAPK signaling in T and B cells. J Exp Med. 2003; 198:1595–1608. [PubMed: 14623913]

49. Cotta-de-Almeida V, et al. Wiskott Aldrich syndrome protein (WASP) and N-WASP are critical for T cell development. Proc Natl Acad Sci U S A. 2007; 104:15424–15429. [PubMed: 17878299]
50. Roy E, et al. Nck adaptors are positive regulators of the size and sensitivity of the T-cell repertoire. Proc Natl Acad Sci U S A. 107:15529–15534. [PubMed: 20709959]
51. Wu Z, et al. Memory T cell RNA rearrangement programmed by heterogeneous nuclear ribonucleoprotein hnRNPLL. Immunity. 2008; 29:863–875. [PubMed: 19100700]
52. Randall KL, et al. Dock8 mutations cripple B cell immunological synapses, germinal centers and long-lived antibody production. Nat Immunol. 2009; 10:1283–1291. [PubMed: 19898472]
53. Jha MK, et al. Defective survival of naive CD8+ T lymphocytes in the absence of the beta3 regulatory subunit of voltage-gated calcium channels. Nat Immunol. 2009; 10:1275–1282. [PubMed: 19838200]
54. Tough DF, Sprent J. Turnover of naive-and memory-phenotype T cells. J Exp Med. 1994; 179:1127–1135. [PubMed: 8145034]
55. Murali-Krishna K, et al. Persistence of memory CD8 T cells in MHC class I-deficient mice. Science. 1999; 286:1377–1381. [PubMed: 10558996]
56. Tanchot C, Lemonnier FA, Pérarnau B, Freitas AA, Rocha B. Differential requirements for survival and proliferation of CD8 naïve or memory T cells. Science. 1997; 276:2057–2062. [PubMed: 9197272]
57. Labrecque N, et al. How much TCR does a T cell need? Immunity. 2001; 15:71–82. [PubMed: 11485739]
58. Polic B, Kunkel D, Scheffold A, Rajewsky K. How alpha beta T cells deal with induced TCR alpha ablation. Proc Natl Acad Sci U S A. 2001; 98:8744–8749. [PubMed: 11447257]
59. Rooke R, Waltzinger C, Benoist C, Mathis D. Targeted complemetation of MHC class II deficiency by intrathymic delivery of recombinant adenoviruses. Immunity. 1997; 7:123–134. [PubMed: 9252125]
60. Surh CD, Sprent J. Regulation of mature T cell homeostasis. Semin Immunol. 2005; 17:183–191. [PubMed: 15826823]
61. Takeda S, Rodewald HR, Arakawa H, Bluethmann H, Shimizu T. MHC class II molecules are not required for survival of newly generated $CD4^+$ T cells but affect their long-term life span. Immunity. 1996; 5:217–228. [PubMed: 8808677]
62. Dorfman JR, Stefanova I, Yasutomo K, Germain RN. CD4+ T cells survival is not directly linked to self-MHC-induced TCR signaling. Nature Immunol. 2000; 1:329–335. [PubMed: 11017105]
63. Grandjean I, et al. Are major histocompatibility complex molecules involved in the survival of naive CD4+ T cells? J Exp Med. 2003; 198:1089–1102. [PubMed: 14517277]
64. Martin B, Bourgeois C, Dautigny N, Lucas B. On the role of MHC class II molecules in the survival and lymphopenia-induced proliferation of peripheral CD4+ T cells. Proc Natl Acad Sci U S A. 2003; 100:6021–6026. Epub 2003 Apr 6028. [PubMed: 12719530]
65. Fischer UB, et al. MHC class II deprivation impairs CD4 T cell motility and responsiveness to antigen-bearing dendritic cells in vivo. Proc Natl Acad Sci US A. 2007; 104:7181–7186.
66. Stefanova I, Dorfman JR, Germain RN. Self-recognition promotes the foreign antigen sensitivity of naive T lymphocytes. Nature. 2002; 420:429–434. [PubMed: 12459785]
67. Hochweller K, et al. Dendritic cells control T cell tonic signaling required for responsiveness to foreign antigen. Proc Natl Acad Sci U S A. 2010; 107:5931–5936. In seeming contrast to the findings of Takada and Jameson (ref #), this paper demonstrates that in situ ablation of CD11c+ DC leads to a marked reduction inresponses of naïve CD4 and CD8 cells to foreign antigens, correlating with reduced expression of TCRζ in these cells. [PubMed: 20231464]
68. Smith K, et al. Sensory adaptation in naive peripheral CD4 T cells. J Exp Med. 2001; 194:1253–1261. [PubMed: 11696591]
69. Bhandoola A, et al. Peripheral expression of self-MHC-II influences the reactivity and self-tolerance of mature CD4(+) T cells: evidence from a lymphopenic T cell model. Immunity. 2002; 17:425–436. [PubMed: 12387737]
70. Jubala CM, et al. MHC-dependent desensitization of intrinsic anti-self reactivity. Cancer Immunol Immunother. 2009; 58:171–185. [PubMed: 18523772]

71. Fink PJ, Bevan MJ. Positive selection of thymocytes. Adv Immunol. 1995; 59:99–133. [PubMed: 7484464]
72. Yachi PP, Ampudia J, Gascoigne NR, Zal T. Nonstimulatory peptides contribute to antigen-induced CD8-T cell receptor interaction at the immunological synapse. Nat Immunol. 2005; 6:785–792. [PubMed: 15980863]
73. Anikeeva N, et al. Quantum dot/peptide-MHC biosensors reveal strong CD8-dependent cooperation between self and viral antigens that augment the T cell response. Proc Natl Acad Sci U S A. 2006; 103:16846–16851. [PubMed: 17077145]
74. Krogsgaard M, et al. Agonist/endogenous peptide-MHC heterodimers drive T cell activation and sensitivity. Nature. 2005; 434:238–243. Epub 2005 Feb 2020. [PubMed: 15724150]
75. Lo WL, et al. An endogenous peptide positively selects and augments the activation and survival of peripheral CD4+ T cells. Nat Immunol. 2009; 10:1155–1161. [PubMed: 19801984]
76. Schluns KS, Lefrancois L. Cytokine control of memory T-cell development and survival. Nat Rev Immunol. 2003; 3:269–279. [PubMed: 12669018]
77. Jacobs SR, Michalek RD, Rathmell JC. IL-7 is essential for homeostatic control of T cell metabolism in vivo. J Immunol. 2010; 184:3461–3469. [PubMed: 20194717]
78. Khaled AR, Durum SK. Lymphocide: cytokines and the control of lymphoid homeostasis. Nat Rev Immunol. 2002; 2:817–830. [PubMed: 12415306]
79. Rathmell JC, Farkash EA, Gao W, Thompson CB. IL-7 enhances the survival and maintains the size of naive T cells. J Immunol. 2001; 167:6869–6876. [PubMed: 11739504]
80. Repass JF, et al. IL7-hCD25 and IL7-Cre BAC transgenic mouse lines: new tools for analysis of IL-7 expressing cells. Genesis. 2009; 47:281–287. [PubMed: 19263498]
81. Shalapour S, et al. Commensal microflora and interferon-gamma promote steady-state interleukin-7 production in vivo. Eur J Immunol. 2010; 40:2391–2400. [PubMed: 20690180]
82. Link A, et al. Fibroblastic reticular cells in lymph nodes regulate the homeostasis of naive T cells. Nat Immunol. 2007; 8:1255–1265. [PubMed: 17893676]
83. Kerdiles YM, et al. Foxo1 links homing and survival of naive T cells by regulating L-selectin, CCR7 and interleukin 7 receptor. Nat Immunol. 2009; 10:176–184. Complementing the paper of Ouyang et al (ref. 84), studies on the effects of deleting Foxo1 in T cells demonstrate that Foxo1 maintains naïve T cell viability by inducing upregulation of IL-7Ra and lymph node homing receptors, CD62L and CCR7. High expression of the latter enables T cells to reach IL-7-rich environments. [PubMed: 19136962]
84. Ouyang W, Beckett O, Flavell RA, Li MO. An essential role of the Forkhead-box transcription factor Foxo1 in control of T cell homeostasis and tolerance. Immunity. 2009; 30:358–371. Along with the paper of Kerdiles et al (ref. 83), Foxo1 deletion in T cells is shown to reduce IL-7Ra expression, leading to reduced numbers of naïve T cells and an increase in activated/memory T cells. The authors suggest that Foxo1 somehow prevents T cell activation by commensal bacteria. [PubMed: 19285438]
85. Gubbels Bupp MR, et al. T cells require Foxo1 to populate the peripheral lymphoid organs. Eur J Immunol. 2009; 39:2991–2999. [PubMed: 19658095]
86. Carlson CM, et al. Kruppel-like factor 2 regulates thymocyte and T-cell migration. Nature. 2006; 442:299–302. [PubMed: 16855590]
87. Bai A, Hu H, Yeung M, Chen J. Kruppel-like factor 2 controls T cell trafficking by activating L-selectin (CD62L) and sphingosine-1-phosphate receptor 1 transcription. J Immunol. 2007; 178:7632–7639. [PubMed: 17548599]
88. Berger M, et al. An Slfn2 mutation causes lymphoid and myeloid immunodeficiency due to loss of immune cell quiescence. Nat Immunol. 11:335–343. [PubMed: 20190759]
89. Berard M, Brandt K, Bulfone-Paus S, Tough DF. IL-15 promotes the survival of naive and memory phenotype CD8+ T cells. J Immunol. 2003; 170:5018–5026. [PubMed: 12734346]
90. Cho JH, et al. An intense form of homeostatic proliferation of naive CD8+ cells driven by IL-2. J Exp Med. 2007; 204:1787–1801. [PubMed: 17664294]
91. Boyman O, Ramsey C, Kim DM, Sprent J, Surh CD. IL-7/Anti-IL-7 mAb Complexes Restore T Cell Development and Induce Homeostatic T Cell Expansion without Lymphopenia. J Immunol. 2008; 180:7265–7275. [PubMed: 18490726]

92. Melchionda F, et al. Adjuvant IL-7 or IL-15 overcomes immunodominance and improves survival of the CD8+ memory cell pool. J Clin Invest. 2005; 115:1177–1187. Epub 2005 Apr 1177. [PubMed: 15841203]

93. Kieper WC, et al. Recent immune status determines the source of antigens that drive homeostatic T cell expansion. J Immunol. 2005; 174:3158–3163. [PubMed: 15749843]

94. Min B, et al. Neonates support lymphopenia-induced proliferation. Immunity. 2003; 18:131–140. [PubMed: 12530982]

95. Boyman O, Cho JH, Tan JT, Surh CD, Sprent J. A major histocompatibility complex class I-dependent subset of memory phenotype CD8+ cells. Journal of Experimental Medicine. 2006; 203:1817–1825. [PubMed: 16818671]

96. Purton JF, et al. Antiviral CD4+ memory T cells are IL-15 dependent. J Exp Med. 2007; 204:951–961. [PubMed: 17420265]

97. Wang Y, Seidl T, Whittall T, Babaahmady K, Lehner T. Stress-activated dendritic cells interact with CD4+ T cells to elicit homeostatic memory. Eur J Immunol. 2010; 40:1628–1638. [PubMed: 20391436]

98. Li O, et al. Massive and destructive T cell response to homeostatic cue in CD24-deficient lymphopenic hosts. J Exp Med. 2006; 203:1713–1720. Epub 2006 Jun 1712. [PubMed: 16769998]

99. Rothlin CV, Lemke G. TAM receptor signaling and autoimmune disease. Curr Opin Immunol. 2010

100. Martin CE, Kim DM, Sprent J, Surh CD. Is IL-7 from dendritic cells essential for the homeostasis of CD4+ T cells? Nat Immunol. 2010; 11:547–548. author reply 548. [PubMed: 20562832]

101. Boyman O, Kovar M, Rubinstein MP, Surh CD, Sprent J. Selective stimulation of T cell subsets withantibody-cytokine immune complexes. Science. 2006; 311:1924–1927. Epub 2006 Feb 1916. [PubMed: 16484453]

102. Weinreich MA, Odumade OA, Jameson SC, Hogquist KA. T cells expressing the transcription factor PLZF regulate the development of memory-like CD8+ T cells. Nat Immunol. 2010; 11:709–716. [PubMed: 20601952]

103. Maroof A, Beattie L, Kirby A, Coles M, Kaye PM. Dendritic cells matured by inflammation induce CD86-dependent priming of naive CD8+ T cells in the absence of their cognate peptide antigen. J Immunol. 2009; 183:7095–7103. [PubMed: 19917700]

104. Probst HC, McCoy K, Okazaki T, Honjo T, van den Broek M. Resting dendritic cells induce peripheral CD8+ T cell tolerance through PD-1 and CTLA-4. Nat Immunol. 2005; 6:280–286. [PubMed: 15685176]

105. Hale JS, Wubeshet M, Fink PJ. TCRrevision generates functional CD4(+) T cells. J Immunol. 2010; 185:6528–6534. [PubMed: 20971922]

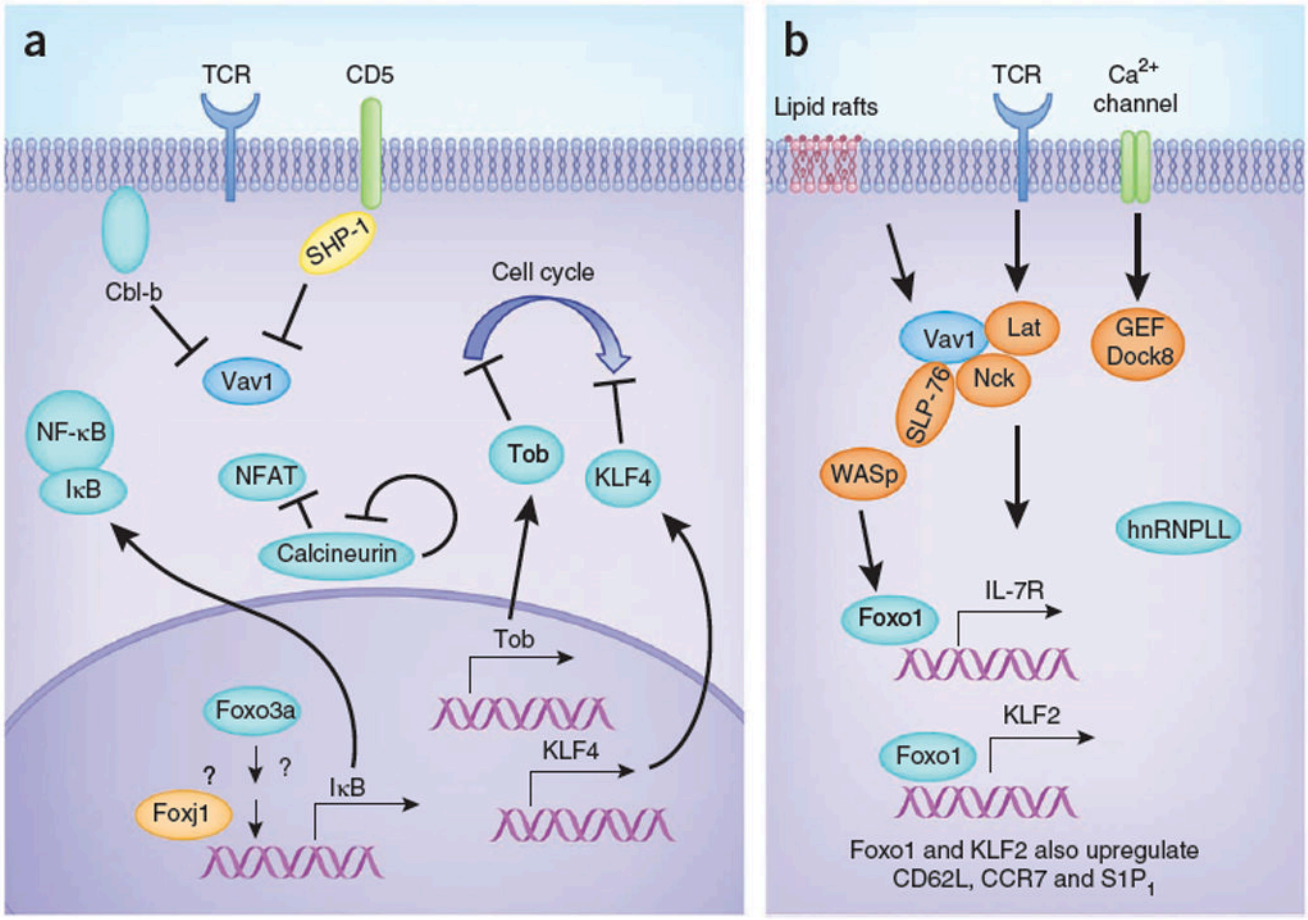

Figure 1.

TCR tuning and signaling pathways involved in maintaining naïve T cell survival in a quiescent state. A) TCR tuning at the proximal stage requires upregulation of negative regulator adapter protein Cbl-b and CD5-associated SHP-1 to block Vav activation. Further downstream, repression of NFκB activity is involved through Foxj1- and Foxo3a-induced synthesis of the NFκB inhibitor, IkB. Inhibition of calcineurin-mediated NFAT translocation to the nucleus is prevented in resting T cells by the autoinhibitory domain of calcineurin. Cell cycle arrest is mediated by a variety of transcription factors, such as Tob and KLF4, which downregulate expression of genes essential for cell cycle progression. B) Several signaling pathways are essential for survival of naïve T cells. Impaired lifespan of naïve T cells is seen in mice lacking Vav1, WASP, the adaptor Nck, the RNA-binding protein, hnRNPLL, a Rho-Rac GTP exchange factor, Dock 8, and the β3 regulatory subunit of voltage-gated calcium channels. Lipid rafts have been shown to enhance TCR signaling and responsiveness to homeostatic cytokines.

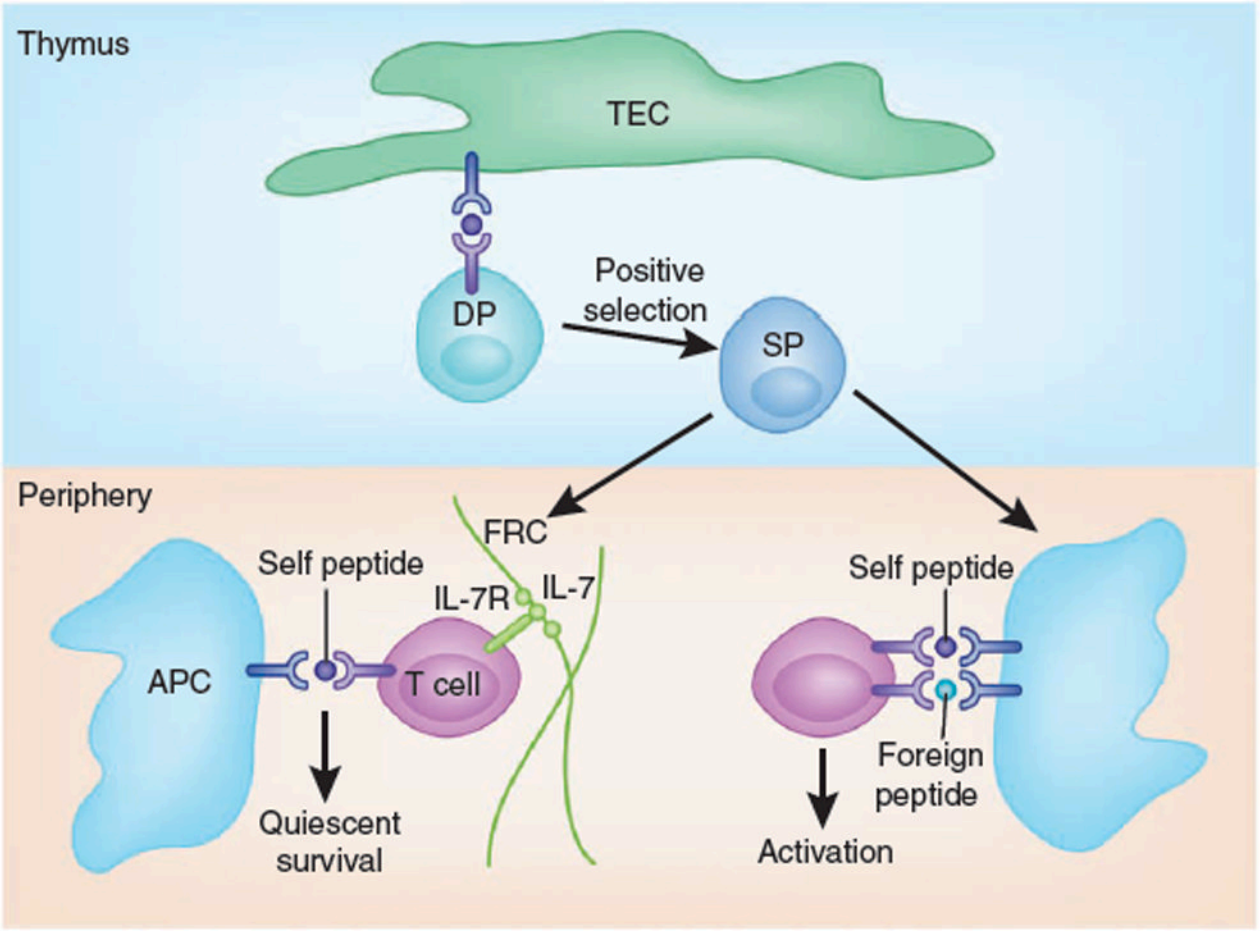

Figure 2.

Positive selection to self-MHC ligands on thymic epithelial cells (TEC) has at least two purposes. First, selection of a T cell repertoire that can react weakly to self-pMHC ligands in the periphery ensures that naïve T cells receive continuous tonic TCR signals; these signals together with recognition of IL-7 on fibroblastic reticular cells (FRC) upregulate expression of anti-apoptotic molecules in T cells and thereby maintain cell survival in interphase. Second, interaction with low-affinity self-pMHC ligands on APCs during the immune response augments TCR signaling induced by high-affinity foreign p-MHC ligands, thereby resulting in strong T cell activation.

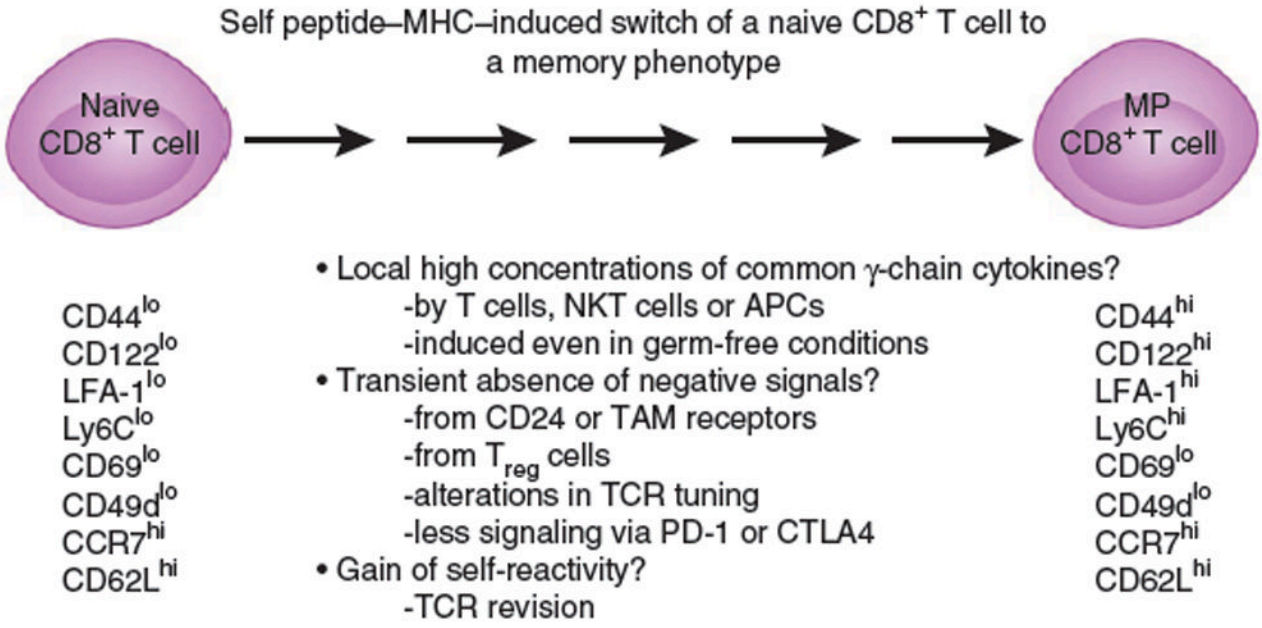

Figure 3.
Possible mechanisms involved in conversion of naïve T cells to memory-phenotype cells under normal physiological conditions. A subset of memory-phenotype cells is activated, fast-dividing cells. The mechanisms shown are largely speculative.