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

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Weak T cell antigen receptor (TCR) signals from contact with self ligands act in synergy with antiapoptotic signals induced by interleukin 7 (IL-7) to promote the survival of naive T cells in a resting state. The amount of background TCR signaling in naive T cells is set by post-thymic TCR tuning and operates at an intensity just below that required to induce entry into the cell cycle. Costimulation from higher concentrations of IL-7 and other common γ-chain cytokines can induce T cells to undergo homeostatic proliferation and conversion into cells with a memory phenotype; many of these memory phenotype cells may be the progeny of cells responding to self antigens. The molecular mechanisms that control the conversion of naive resting T cells into memory-phenotype cells TCR-dependent in normal animals are beginning to be understood.

The pool of mature αβ T cells positive for the T cell antigen receptor (TCR^+) in the secondary lymphoid organs is generated through slow release of young cells from the thymus[1,2]; formation of the T cell pool occurs largely in early life but continues into old age. T cell differentiation in the thymus involves a stringent process of selection during which immature $CD4^+CD8^+$ double-positive T cells are screened for TCR reactivity to self peptides bound to major histocompatibility complex (MHC) molecules[3]. Cells with high avidity for these ligands are deleted (negative selection), whereas cells with low but sufficient affinity receive a weak TCR signal that induces the double-positive cells to survive and to differentiate into mature $CD4^+CD8^-$ and $CD4^-CD8^+$ single-positive T cells through contact with MHC class II and MHC class I molecules, respectively (positive selection). Most double-positive cells (around 98%) have negligible affinity for the MHC-peptide complexes in the thymus, and these cells die rapidly *in situ* from neglect (lack of a TCR signal).

Mature $CD4^+$ cells and $CD8^+$ cells in the extrathymic environment are long-lived cells that can remain in interphase for many weeks or months[4,5]. Especially in young life, typical mature resting T cells have a naive phenotype characterized by low expression of CD44 ($CD44^{lo}$) and high expression of the lymph node–homing receptors CD62L and CCR7 ($CD62L^{hi}CCR7^{hi}$). These cells are kept alive by contact of the TCR with ligands of self peptide–MHC plus exposure to interleukin 7 (IL-7)[1,2]. When naive 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 mice. Such memory-phenotype T cells account for 10–20% of T cells in young mice but increase to large numbers in old age.

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

The origin of memory-phenotype cells

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

It is clear that typical memory-phenotype T cells arise in large numbers when naive T cells are transferred to lymphopenic hosts[1,2,12]. The extensive homeostatic proliferation of naive T cells in lymphopenic hosts applies to both polyclonal and TCR-transgenic cells and is directed to various self peptide–MHC complexes; this 'anti-self' response is boosted by the higher concentration of IL-7 in lymphopenic hosts[1,2,13,14]. As the memory-phenotype cells generated in lymphopenic conditions closely resemble the memory-phenotype cells found in normal mice, it has been suggested that most naturally occurring memory-phenotype cells arise from homeostatic proliferation elicited by contact with self ligands[2,4,15]. Strong support for this idea has been provided by studies of the antigen-specificity of

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memory-phenotype T cells[16,17]. The use of specific tetramers of peptide and MHC class I to detect reactive CD8+ T cells has shown that contrary to previously published results[18], 10–30% of antigen-specific T cells in normal unimmunized mice have a CD44^{hi} phenotype. That finding is unlikely to reflect cross-reactive responses to environmental antigens because the data apply 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 considerable proportion of the T cells found in many unmanipulated TCR-transgenic lines, including mice on a RAG recombinase–deficient background[16]. Most of the tetramer-binding CD44^{hi} memory-phenotype T cells in this study had the typical phenotype of resting central memory cells but differed from these cells in having only low expression of CD49d (α_4 integrin). As the bulk of CD44^{hi}CD8+ T cells in normal mice are CD49d^{lo} cells, the authors concluded that most naturally occurring memory-phenotype cells arise from cells undergoing homeostatic proliferation in response to self ligands[16].

The data indicating self antigens are the stimulus for the generation of memory-phenotype cells have relied heavily on studies of CD8+ T cells. CD4+ T cells are less sensitive to homeostatic proliferation than are CD8+ T cells[1,14,19], and the origin of memory-phenotype CD4+ T cells may be more complex. Thus, nearly all of the specific peptide-binding CD4+ T cells in unimmunized mice are typical naive CD44^{lo} cells[20].

For CD8+ T cells, the antigen-specific memory-phenotype cells found in normal mice differ from naive cells in having rapid proliferative responses to antigens and substantial production of interferon-γ in response to inflammatory cytokines[16]. Hence, memory-phenotype cells may have a vital role in the early stages of the immune response to pathogens for both innate and adaptive responses. This function could be especially important when efficient immune responses are essential, such as in the neonatal period and old age. In this context, it is of interest that memory-phenotype cells are prominent in both of these stages, with memory phenotype production in neonatal mice reflecting T lymphopenia in young life.

TCR tuning and the maintenance of naive T cells

Although the physiological purpose of positive selection has long been debated, it is now thought that the selection of T cells for weak reactivity to self peptides in the thymus allows the cells to engage in continuous, low-intensity TCR interaction with these same or cross-reactive peptides in the periphery[1,4,21]. This interaction provides naive T cells with tonic TCR signals that, in conjunction with IL-7, maintain cell viability by promoting the expression of prosurvival molecules such as Bcl-2. As naive 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 double-positive cells in the thymus is associated with upregulation of CD69, an activation marker, whereas mature extrathymic T cells do not express this marker unless activated with antigen[3]. Also, double-positive cells are more sensitive to activation by antigen than mature T cells[3,22], which correlates with the higher expression by double-positive cells of the micro-RNA miR-181a, a phosphatase regulator[23].

Those and other findings indicate that after positive selection, T cells undergo a process of TCR desensitization before entering the secondary lymphoid tissues[24,25]. This '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 diminishes TCR signaling to just below the amount required for entry into the 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 the fact that lymphopenia results in a predisposition to the development of autoimmune disease; thus, homeostatic proliferation directed to ubiquitous weak self peptides might activate autoaggressive T cells with cross-reactive specificity for sequestered antigens—the targets for autoimmune disease[4]. High sensitivity to homeostatic proliferation applies to many TCR-transgenic lines, but such sensitivity 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 on either epithelial cells or dendritic cells[28]. For high-affinity T cells, TCR tuning involves the upregulation of molecules that limit TCR responsiveness, notably the ubiquitin ligase Cbl-b (which blocks activation of the adaptor Vav[29–31]), the tyrosine phosphatase SHP-1 (ref. 28) and CD5 (which is constitutively associated with SHP-1 (refs. 32,33); **Fig. 1a**). TCR tuning by CD5 has elicited particular interest because surface expression of CD5 correlates directly with the intensity of homeostatic proliferation. Thus, CD8+ TCR-transgenic lines with high sensitivity to homeostatic proliferation in lymphopenic hosts, such as the OT-I and 2C cell lines, have a CD5^{hi} phenotype, whereas cells from lines that fail to undergo homeostatic proliferation, such as HY cells, are CD5^{lo} cells[27]. Likewise, purified subsets of polyclonal CD5^{hi} cells from normal mice show stronger homeostatic proliferation responses than do CD5^{lo} cells[19]. As well as increasing the expression of negative regulators, TCR tuning is associated with altered expression of various cell-surface molecules that have costimulatory functions, including CD2 (ref. 34) and CD8, which enhances interactions between TCR and MHC class I (refs. 35–37).

Maintaining naive T cells in a quiescent state is a complex process that requires the interaction of many different negative regulatory mechanisms that prevent cell activation[38] (**Fig. 1a**). Repression of the activity of the transcription factor NF-κB is especially important and involves continuous synthesis of the NF-κB inhibitor IκB by two members of the forkhead family of transcription factors, Foxo3a and Foxj1. The expression of Foxo3a and Foxj1 is high in naive T cells, and their deletion causes pathology through hyperproliferation of T cells[39,40], although the data about Foxo3a are contentious[41,42]. T cell quiescence also depends on continuous inactivation of the transcription factor NFAT. Calcineurin-mediated dephosphorylation of NFAT and its translocation to the nucleus is prevented in resting T cells by the autoinhibitory domain of calcineurin[38]. Nevertheless, NFAT can also maintain the resting status of T cells by repressing the cell-cycle activator Cdk4; thus, mice deficient in NFAT1 (*Nfatc2*$^{-/-}$) develop splenomegaly and signs of T cell activation, which correlates with higher concentrations of Cdk4 protein[43,44]. In this context, T cell quiescence requires the presence of a variety of transcription factors that downregulate the expression of genes that are essential for cell-cycle progression, such as Cdk2, or cause upregulation of p27^{Kip1}, a negative regulator of the cell cycle. One such factor is Tob, which has high expression in naive T cells[45] and may be maintained by the transcription factor, KLF2 (LKLF). Thus, KLF2-deficient T cells show hyperproliferation and expression of activation markers[46,47]; however, KLF2 deficiency can have other effects on T cells (discussed below). For CD8+ T cells, quiescence of naive cells also involves two other transcription factors, ELF4 and KLF4 (ref. 48). The results of studies of *Elf4*$^{-/-}$ CD8+ T cells suggest that ELF4 activates KLF4 and that this diminishes TCR sensitivity, perhaps through 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 single-positive thymocytes, after conditional deletion of Foxp1 in double-positive thymocytes[49]. How Foxp1 induces quiescence is unclear.

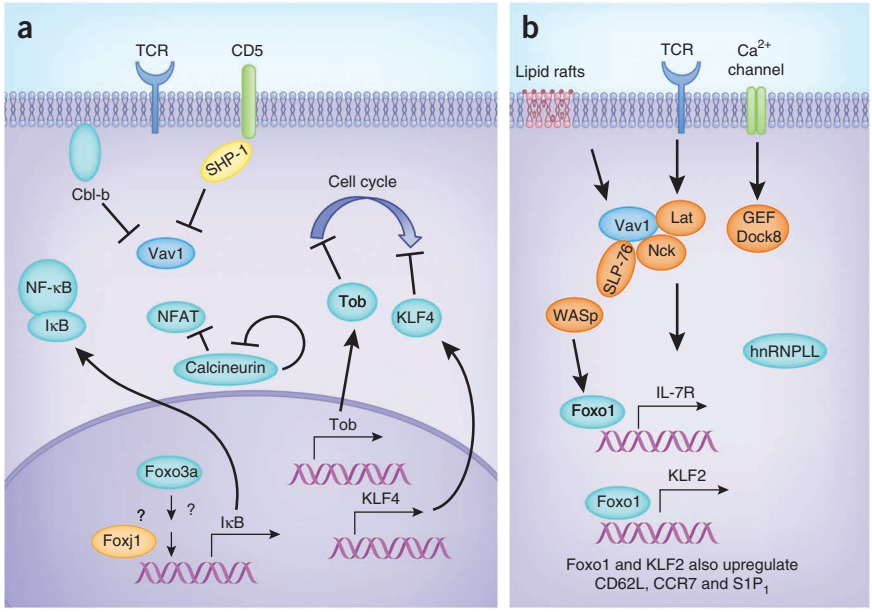

Figure 1 TCR tuning and signaling pathways involved in maintaining the survival of naive T cells in a quiescent state. (**a**) TCR tuning at the proximal stage requires upregulation of Cbl-b and CD5-associated SHP-1 to block Vav activation. Further downstream, repression of NF-κB activity could occur through Foxj1- and Foxo3a-induced synthesis of IκB. Inhibition of calcineurin-mediated translocation of NFAT 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 the expression of genes essential for cell-cycle progression. (**b**) Signaling pathways essential for the survival of naive T cells. Naive T cells have a shorter lifespan in mice lacking Vav1, Wiskott-Aldrich syndrome protein (WASp), the adaptor Nck, the RNA-binding protein hnRNPLL, a Rho-Rac GTP-exchange factor (GEF), Dock8 or the β3 regulatory subunit of voltage-gated calcium channels. Lipid rafts have been shown to enhance TCR signaling and responsiveness to homeostatic cytokines. SLP-76, adaptor; Lat, transmembrane signaling protein.

Tonic TCR signaling of T cells is vital for the maintenance of cell viability (**Fig. 1b**). This is apparent from the finding that deletion or mutation of genes encoding various molecules involved in TCR signaling can shorten the lifespan of naive T cells *in vivo*. Thus, diminished survival of naive T cells is seen in mice lacking Vav1 (ref. 50), Wiskott-Aldrich syndrome protein[51], the adaptor Nck[52], the RNA-binding protein hnRNPLL[53], the Rho-Rac GTP-exchange factor Dock8 (ref. 54) or the β3 regulatory subunit of voltage-gated calcium channels[55]. In these various situations, the shorter lifespan of naive T cells generally correlates with TCR hyporesponsiveness.

Effects of depriving T cells of MHC contact

Normal naive T cells can survive in interphase for prolonged periods—months in mice, and years in humans[5,56]. It is well accepted that depriving mouse $CD8^+$ T cells of contact with MHC class I molecules[57,58] or ablating TCR expression[59,60] causes naive cells to die within several weeks. In those studies, the half-life of the cells ranged from 2–7 days for naive cells transferred to MHC class I–deficient hosts to 16–19 days after TCR ablation. For T cell–transfer studies, the presence of MHC class I on the transferred cells and the use of lymphopenic hosts could complicate the results. Such problems were avoided in a study in which MHC class I–deficient $CD8^+$ T cells prepared from bone marrow chimeras were transferred to nonlymphopenic MHC class I–deficient hosts[37]. Under these conditions, the half-life of naive $CD8^+$ cells was about 10 days.

The situation with $CD4^+$ T cells is distinctly different. Indeed, despite intensive investigation, the influence of the TCR–MHC class II interaction on the survival of naive $CD4^+$ T cells remains unresolved. In some studies, $CD4^+$ T cells disappear quite rapidly after being transferred to MHC class II–deficient hosts[61–63], whereas in other studies naive $CD4^+$ T cells survive as resting cells for prolonged periods[64,65]. However, the hosts used for some of the second group of studies were lymphopenic and therefore had higher concentrations of cytokines, or the hosts may have had residual expression of MHC class II in the form of heterodimers of the Aα and Eβ chains of MHC[66]. After TCR ablation *in situ*, the half-life of naive $CD4^+$ T cells varies from about 27 d (ref. 59) to 46 d (ref. 60), relative to 78 d for normal cells. As a whole, the data suggest that CD4 cells do depend on MHC class II contact for their survival but probably less so than $CD8^+$ T cells do. Furthermore, $CD4^+$ T cells in MHC class II–deficient hosts show impaired cell motility and less ability to interact with dendritic cells[67]. It was concluded that tonic TCR signaling by ligands of self MHC class II maintains cell motility by promoting basal activation of the GTPases Rap1 and Rac1.

Tonic TCR signaling may also be beneficial in promoting responsiveness to foreign antigens. Depriving $CD4^+$ T cells of contact with MHC class II induces a rapid decrease in phosphorylation of TCRζ and lower responses to foreign antigens[68]. Similar effects occur after selective ablation of $CD11c^+$ dendritic cells *in situ* through use of the CD11c.DOG mouse system, for both $CD4^+$ and $CD8^+$ T cells[69]. Despite those findings, there is also evidence that loss of MHC contact can lead to partial reversal of TCR tuning and an increase in responsiveness to antigens. For TCR tuning, CD5 concentrations decrease in both $CD8^+$ T cells[37] and $CD4^+$ T cells[60,67,70] after T cells are transferred to hosts deficient in MHC class I and MHC class II, thereby lessening the negative effects of CD5 on TCR signaling. Likewise, 'parking' $CD8^+$ T cells in MHC class I–deficient hosts leads to higher cell-surface expression of CD8, paralleled by lower expression of the IL-7 receptor α-chain (IL-7Rα)[37]. This reversal of TCR tuning is reported to cause $CD8^+$ T cells to show more TCR reactivity to weak TCR agonists (but not to strong TCR agonists). The results for $CD4^+$ T cells are less clear-cut[2], although in some studies depriving these cells of MHC class II contact causes more TCR responsiveness, as defined by greater Ca^{2+} responses after TCR ligation[70] and the ability to reject syngeneic MHC class II–positive skin grafts[71]. Likewise, unseparated T cells transferred to hosts with combined double deficiency in MHC class I and MHC class II acquire the ability to reject grafts of syngeneic normal pancreas[72]. Although they are 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 MHC Aα-Eβ heterodimers. This concern does not apply to the experiments on $CD8^+$ T cells because nonlymphopenic hosts were used for these studies.

The observation that naive $CD8^+$ T cells 'parked' in MHC class I–deficient hosts acquire greater 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

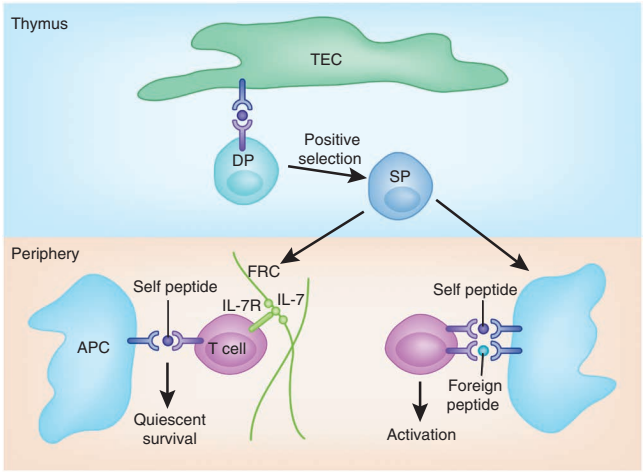

Figure 2 Positive selection in the thymus. Positive selection to ligands of self peptide–MHC on thymic epithelial cells (TEC) has at least two purposes. First, selection of a T cell repertoire that can react weakly to self peptide–MHC ligands in the periphery ensures that naive T cells receive continuous tonic TCR signals; these signals, together with recognition of IL-7 on fibroblastic reticular cells (FRC) in the periphery, upregulate expression of antiapoptotic molecules in T cells and thereby maintain cell survival in interphase. Second, interaction with low-affinity self peptide–MHC ligands on antigen-presenting cells (APC) during the immune response augments TCR signaling induced by high-affinity foreign peptide–MHC ligands, thereby resulting in strong activation of T cells. DP, double-positive; SP, single positive.

explanation was that positive selection to self components increases the capacity of T cells to respond to foreign antigens[73]. But precisely how self-recognition could improve responses to foreign antigens has never been explained clearly. So interest has now switched to the idea that the main purpose of positive selection is to guide T cell survival in the post-thymic environment[4]. However, in reconsidering the original explanation, it is notable that T cell responses to foreign peptides are augmented by the presence of low-affinity nonstimulatory peptides[74–77]. It is worth recalling that the initial findings on positive selection were provided by studies of MHC-heterozygous $(A \times B)F_1 \rightarrow$ parent bone marrow chimeras showing that F_1 T cells that differentiate in the thymus of parent A provide better responses to foreign antigens presented by parent A than to those 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 peptide–MHC ligands somehow enhances reactivity to foreign peptides. However, given the newer data on the augmenting role of nonstimulatory peptides for optimal T cell responses, it can be argued that the main purpose of positive selection is to generate a repertoire of T cells with substantial TCR-binding affinity for the weak MHC-associated self peptides on normal antigen-presenting cells, with such recognition serving to augment interactions between T cells and antigen-presenting cells and thereby to enhance contact of TCRs with foreign peptides (**Fig. 2**). This idea is a variation on the previous suggestion that the tonic TCR signals that result from self-recognition maintain TCR sensitivity to foreign antigens[68]. Both models are compatible with the view that recognition of self peptide can have other functions; that is, providing a stimulus for T cell survival[1] (**Fig. 2**).

Role of cytokines

By itself, tonic TCR signaling is not sufficient to keep naive T cells alive. The cells also must make contact with common γ-chain cytokines such as IL-7 (refs. 1,78). Thus, naive $CD4^+$ T cells and $CD8^+$ T cells die within 1–2 weeks of transfer into *Il7*$^{-/-}$ hosts[1,78] or after conditional deletion of *Il7r*[79]. Binding of IL-7 to IL-7R promotes survival by upregulating the expression of antiapoptotic molecules, especially Bcl-2 and Mcl-1 (ref. 80). However, IL-7 also has an important role in maintaining normal cell metabolism because, in addition to diminishing lifespan, conditional deletion of *Il7r* causes naive T cells to decrease in size and fail to maintain a basal rate of glycolytic flux[79,81]. IL-7 also has other effects on T cells, notably maintaining the expression of CD8 and modulating the expression of IL-7Rα, a process called 'coreceptor tuning'[36]. IL-7 is synthesized largely by $CD45^-$ stromal cells and is most prominent in the thymus, lymph nodes and bone marrow[82–84].

As mentioned above, IL-7 responsiveness is controlled by an autocrine loop in which signaling by IL-7R limits the transcription of *Il7r*[85]. However, the factors that control responsiveness to IL-7 are complex and involve the interaction of many transcription factors. For naive T cells, the influence of the Foxo subfamily of forkhead transcription factors, especially Foxo1, is particularly important[86–88]. Thus, conditional deletion of Foxo1 in T cells leads to a much lower expression of IL-7Rα associated with less Bcl-2 and a paucity of naive T cells; Foxo1 seems to maintain IL-7Rα expression by binding to the proximal *Il7r* promoter. Interestingly, in addition to controlling IL-7R expression, Foxo1 maintains the upregulation of several molecules involved in T cell homing: CD62L, CCR7 and $S1P_1$. Expression of these molecules is much lower in naive *Foxo1*$^{-/-}$ T cells; this reflects the fact that Foxo1 binds to the promoter for the gene encoding KLF2, which is known to guide CD62L and $S1P_1$ expression[89,90]. The control of T cell–homing receptors by Foxo1 might be crucial for the migration of naive cells to the main sites of IL-7 synthesis; that is, the T cell areas in lymph nodes. Further information about the control of IL-7 responsiveness has been provided by studies of Slfn2, a member of the Schlafen family of transcription factors[91]. Mice with *Slfn2* mutations have fewer naive T cells, poor responsiveness to IL-7 and greater sensitivity to apoptotic signals. Although the functions of Slfn2 are unclear, it may be relevant that the mutant cells have low expression of CD62L and IL-7Rα. Hence, like Foxo1, Slfn2 may act in part by controlling responsiveness to IL-7.

Under physiological conditions, the continuous interaction of naive T cells with cytokines seems to be limited to IL-7. However, optimal survival of naive $CD8^+$ T cells also requires joint contact with IL-15; thus, the number of naive $CD8^+$ T cells (but not $CD4^+$ T cells) is slightly lower in *Il15*$^{-/-}$ mice[92]. Nevertheless, naive cells do respond to higher concentrations of other γ-chain cytokines, especially IL-2. In fact, exposing $CD8^+$ T cells to high concentrations of IL-2 (or IL-15) induces vigorous proliferation of naive cells, both *in vivo* and *in vitro*[93]; proliferation of $CD4^+$ T cells is much lower, which correlates with expression of CD122, the β-chain of the IL-2 and IL-15 receptor, being low on naive $CD8^+$ T cells but undetectable on $CD4^+$ T cells.

We mentioned earlier that a notable feature of IL-7-dependent homeostatic proliferation in lymphopenic hosts is that naive $CD8^+$ T cells generally proliferate much more rapidly than $CD4^+$ T cells do[14,26]. Likewise, proliferation induced by injection of exogenous IL-7 (or IL-2) is more intense for $CD8^+$ T cells than for $CD4^+$ T cells[94,95]. This difference does not reflect IL-7R expression because both T cell subsets show the same density of IL-7R. The enhanced sensitivity of $CD8^+$ T cells to cytokines has been found to correlate with cell-surface expression of lipid rafts, as measured by staining of GMI ganglioside[19]. Thus, as defined by surface staining of GMI, $CD8^+$ T cells have higher expression of lipid rafts than do $CD4^+$ T cells. Lipid raft expression on $CD8^+$ T cells is induced at a late stage in positive

selection and correlates directly with cytokine responsiveness and CD5 concentrations, with GM1^{hi}CD5^{hi} cells being more sensitive to IL-7 and other γ-chain cytokines than are GM1^{lo}CD5^{lo} cells.

TCR control of cytokine responsiveness

It is unclear why naive T cells require both TCR signaling and cytokine contact to remain alive. For cytokines, IL-7 is presumed to function simply by maintaining expression of Bcl-2. However, how tonic TCR signals promote cell viability is a mystery. One possibility is that instead of directly inducing expression of prosurvival molecules, the weak TCR signals that result from interactions with self peptide–MHC ligands function indirectly by augmenting responsiveness to cytokines. In support of this idea, 'parking' naive CD8$^+$ T cells in an MHC class I–deficient environment causes a rapid loss of sensitivity to γ-chain cytokines, which correlates with lower GM1 expression[19]. This indicates that the main purpose of TCR tuning may be to modulate the sensitivity of mature T cells to cytokines. This idea will require further investigation.

Conversion of naive T cells to memory-phenotype cells

In the many situations in which interfering with tonic TCR signaling leads to a decrease in the number of naive T cells, there is generally a reciprocal increase in the number of memory-phenotype cells. In part, the generation of these cells may reflect homeostatic proliferation due to lymphopenia. But lymphopenia can also results in a predisposition to infection and thereby induce naive T cells to respond to a variety of environmental antigens, thus generating antigen-specific memory cells. Here the effects of transferring naive T cells into lymphopenic hosts deficient in the RAG recombinase or hosts with severe combined immunodeficiency is instructive. In these hosts, most donor cells undergo a pattern of slow proliferation typical of IL-7-induced homeostatic proliferation. However, a small proportion of the cells divide rapidly and soon account for the majority of the proliferating cells. Importantly, these fast-dividing cells are much less frequent in germ-free hosts with severe combined immunodeficiency[96]. Hence, many of the activated and memory T cells that are generated under lymphopenic conditions may arise from cells responding to foreign antigens; this is especially likely in hosts with chronic lymphopenia, which are highly prone to infection. Nevertheless, some of the fast-dividing cells in lymphopenic hosts may be bystander naive T cells driven by the high concentrations of γ-chain cytokines released by the antigen-reactive T cells in these hosts[96]. This scenario may apply to the rapid T cell turnover seen in neonatal mice[97].

As mentioned earlier, cells with features of antigen-specific activated and resting memory T cells are found in normal immunocompetent adult mice, including germ-free and antigen-free mice. Therefore, many of these memory-phenotype cells seem to be the progeny of cells responding to ligands of self peptide–MHC. For both CD4$^+$ T cells and CD8$^+$ T cells, around one-third of memory-phenotype cells have a rapid rate of turnover and express markers of activated T cells[56,98,99]. These cells disappear or revert to resting cells after transfer into MHC-deficient hosts, which indicates that the cells are proliferating in response to MHC-associated peptides, presumably mostly self peptides. Some of these cells survive to form resting memory-phenotype cells but many die rapidly; this is probably because the proportion of resting memory-phenotype cells remains relatively constant during young adult life.

It is unclear why a proportion of naive T cells undergoes steady-state proliferation and differentiation into memory-phenotype cells in response to self ligands in normal unimmunized mice (**Fig. 3**). It is likely that proliferation is initiated by transient increases in the concentration of one or more γ-chain cytokines, such as IL-7, IL-2 or IL-15. That idea fits with the finding that naturally occurring memory-phenotype cells closely resemble the progeny of cells that respond to IL-7 during homeostatic proliferation or after exposure to exogenous IL-2 or IL-15. On this point, it is of interest that brief exposure of dendritic cells to mild thermal stress (culture for 90 min at 41.5 °C) causes cell-surface expression of the heat-shock protein HSP70, activation of NF-κB and more IL-15 synthesis[100]. Under normal conditions, it can be envisaged that stringent immunoregulatory mechanisms are necessary to limit the synthesis of IL-15 and other stimulatory cytokines by dendritic cells and macrophages. Here signaling by the heat-stable antigen CD24 (ref. 101) and also the receptors Tyro3, Axl, and Mer (TAM) for the ingestion of apoptotic cells[102] could be important because mice lacking these molecules show massive lymphadenopathy. Greater responsiveness to IL-7 might reflect dysregulation by a population of IL-7Rα$^+$ dendritic cells[14], although this idea has been disputed[103]. Low concentrations of IL-2 are synthesized constitutively in normal mice[104] and might reach a high concentration in certain microenvironments, perhaps reflecting intermittent synthesis by autoaggressive T cells. For IL-4, it is notable that hyperproliferation and the generation of large numbers of memory-phenotype cells are features of both *Klf2*$^{-/-}$ mice and mice deficient in the tyrosine kinase Itk (*Itk*$^{-/-}$)[105]. The memory-phenotype 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 memory-phenotype cells are much more abundant in this strain than in other mouse strains.

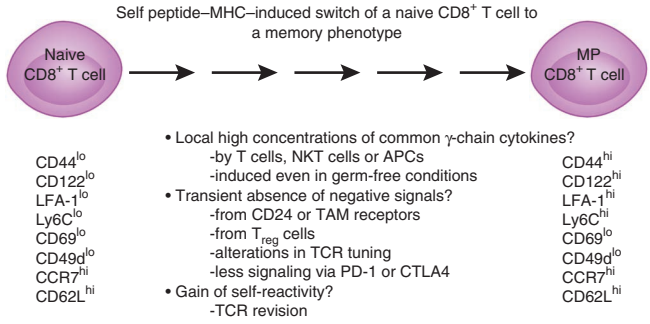

Figure 3 Possible mechanisms involved in conversion of naive T cells to the memory phenotype under normal physiological conditions. A subset of memory-phenotype (MP) cells is composed of activated, fast-dividing cells. These mechanisms are largely speculative.

In addition to involving contact with cytokines, the switch of naive T cells into the memory phenotype may involve other mechanisms, such as transient loss of contact with the inhibitory action of regulatory T cells or subtle alterations in the intensity of tonic TCR signaling (**Fig. 3**). For the latter mechanism, naive T cells are reported to proliferate and form memory-phenotype cells in a bystander manner after exposure to pathogen-activated dendritic cells, which may reflect more self recognition due to enhanced costimulation[106]. A switch to a memory phenotype might also reflect a transient loss of negative signaling in naive cells resulting from interruption of contact between the negative regulatory molecules PD-1 or CTLA-4 on T cells and their respective ligands on dendritic cells[107]. Another possibility is that memory-phenotype cells arise in part through generation of a new TCR by 'TCR revision' after contact with self antigens[108]; on

this point, it is of interest that post-revision T cells have a high rate of turnover. Despite these various possibilities, clear understanding of the mechanisms that guide the background generation of memory-phenotype cells will require further investigation. To avoid the problem of responses to environmental antigens, it will be important to obtain detailed information about memory-phenotype cells generated under germ-free—and optimally antigen-free—conditions.

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