

# Homeostasis of Naive and Memory T Cells

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The peripheral mature T cell pool is regulated by complex homeostatic mechanisms. Naive T cells are maintained by interleukin-7 (IL-7) and T cell receptor (TCR) signaling from contact with major histocompatibility complex (MHC), which sustain expression of antiapoptotic molecules and allow the cells to survive in interphase. Competition for these ligands declines when T cell numbers are reduced and causes residual naive T cells to proliferate and differentiate into memory-like cells. This memory cell population is thus heterogeneous and comprised of cells derived from responses to both foreign and self-antigens. Typical memory cells are kept alive and induced to divide intermittently by a mixture of IL-7 and IL-15. This review highlights recent advances in how naive and memory T cell homeostasis is regulated.

## Introduction

The combined processes of positive and negative selection in the thymus allow a tiny fraction of immature thymocytes with low affinity for self-peptide+MHC (pMHC) ligands to survive and differentiate into mature T cells (Starr et al., 2003). Newly generated T cells exit the thymus to form the long-lived pool of naive T cells that recirculate within the confines of the peripheral lymphoid tissues. Post-thymic T cells retain a low degree of self-reactivity; this reactivity is generally not sufficient to cause autoimmunity, but is essential for survival of naive T cells and also enhances TCR sensitivity for foreign Ags (Krogsgaard et al., 2007). Activation by foreign Ags expressed by pathogens induces naive T cells to undergo massive expansion for several days, with the accompanying acquisition of the appropriate effector functions required for elimination of the pathogen concerned (Harty and Badovinac, 2008; Sprent and Surh, 2002). Most effector cells die off within the next few weeks, but a small fraction of the cells survive almost indefinitely as memory T cells.

As with other cell types in the body, the survival and composition of the mature T cell pool are governed by complex homeostatic mechanisms (Jameson, 2002; Surh and Sprent, 2005). Work from the past several years has led to the discovery that T cell homeostatic signals are largely a consequence of contact with self-pMHC complexes and members of the common gamma chain ( $\gamma_c$ ) family of cytokines, especially IL-7 and IL-15. In the case of naive T cells, prolonged survival of these cells in interphase is dependent on a combination of covert TCR signaling from interaction with self-pMHC ligands plus interaction with IL-7 and to a lesser degree IL-15. By contrast, most memory T cells are MHC independent but rely heavily on contact with a mixture of IL-7 and IL-15, both for their survival and intermittent "homeostatic" proliferation; IL-7 controls cell survival whereas IL-15 elicits proliferation (although these functions are partly overlapping). In young individuals where the thymus is large, the peripheral T cell pool consists mostly of newly formed naive T cells. In later life, atrophy of the thymus reduces production of new T cells, and continuous exposure to a spectrum of environmental Ags shifts the composition of the T cell pool from naive cells to a predominance of memory T cells.

## Naive T Cell Homeostasis and the Role of TCR Signaling

The requirement for TCR signaling was discovered more than 10 years ago with the demonstration by several groups that the lifespan of naive CD4<sup>+</sup> and CD8<sup>+</sup> T cells is shortened when these cells are deprived of contact with self-MHC molecules (Takeda et al., 1996; Tanchot et al., 1997a). For CD4<sup>+</sup> T cells, however, adoptive transfer studies of other groups failed to find a role for MHC on survival (Dorfman et al., 2000; Grandjean et al., 2003). Nonetheless, subsequent studies that used three different approaches have provided further strong support for the idea that naive T cells require TCR signaling for their survival.

First, with the use of a genetically manipulated inducible system, it was found that abrogation of TCR expression or of TCR-proximal tyrosine kinases Fyn and Lck expression within mature T cells caused a reduction in the lifespan of both CD4<sup>+</sup> and CD8<sup>+</sup> naive T cells (Labrecque et al., 2001; Polic et al., 2001; Seddon and Zamoyska, 2002b). One caveat with this approach is that the TCR may transmit covert tonic signaling without having to engage the MHC molecules. Second, although polyclonal naive T cells are known to compete with each other for survival and homeostatic proliferation, such competition does not apply among TCR transgenic T cells with different specificity, suggesting that recognition of specific self-pMHC ligands is required for naive T cell homeostasis (Kieper et al., 2004; Moses et al., 2003). Third, and most importantly, it was recently found that naive TCR transgenic CD4<sup>+</sup> T cells display a short lifespan when adoptively transferred in large numbers into normal syngeneic hosts, but a prolonged lifespan when transferred in very low numbers, i.e., in a situation where their precursor frequency resembles the very small clonal frequency of cells in a polyclonal repertoire (Hataye et al., 2006). Detection of very low numbers of clones was made possible by the ingenious approach of enriching for Ag-specific T cells with pMHC tetramer plus magnetic beads, thereby allowing rapid analysis of the entire T cell pool in the secondary lymphoid tissues for direct measurement of the precursor frequency of Ag-specific T cells in a normal polyclonal repertoire (Hataye et al., 2006). This approach also revealed that the precursor frequency of polyclonal naive T cells specific for a particular foreign Ag is ~20–200 cells/mouse for CD4<sup>+</sup> T cells and slightly higher for

CD8<sup>+</sup> T cells (Hataye et al., 2006; Moon et al., 2007; Obar et al., 2008), confirming the measurements obtained from previous indirect studies (Blattman et al., 2002; Butz and Bevan, 1998). The failure of a large precursor frequency of a particular clone to survive *in vivo* strongly suggests that recognition of specific and limited self-pMHC ligands is required for naive T cell survival. Accordingly, the TCR diversity of the naive T cell pool appears to be established by low-affinity positive selection in the thymus combined with continual peripheral selection via TCR-mediated survival signals resulting from contact with an extremely diverse repertoire of self-pMHC ligands.

The downstream TCR intracellular signaling events required for T cell survival are poorly understood. For naive T cells undergoing slow homeostatic proliferation to the elevated amounts of IL-7 in lymphopenic hosts, microarray analysis revealed a similar profile of genes as for cells undergoing full activation to foreign Ag, although the degree of induction was much lower and there was a paucity of genes associated with effector activity (Goldrath et al., 2004). This finding implies that T cell survival is mediated by typical signaling pathways downstream of TCR and IL-7R, except that these pathways are presumably induced to a very low degree and are received continuously. A few recent reports illustrate this point. First, T cells have been found to require expression of coronin-1, an actin-associated accessory protein that is expressed primarily in hematopoietic cells and negatively regulates the formation of actin filaments. Importantly, coronin-1 is essential not only for T cell migration and activation, but also for their survival (Foger et al., 2006; Haraldsson et al., 2008; Mueller et al., 2008). Thus, coronin-1 mutant mice showed a marked reduction in numbers of naive T cells as the result of spontaneous apoptosis, even though T cell production in the thymus was relatively normal. Coronin-1 mutant naive T cells were also impaired in their ability to undergo rapid proliferation in response to strong mitogenic signaling through CD3 and displayed impaired homeostatic proliferation in lymphopenic hosts, even though signaling through IL-7R was intact. Whereas the increase in death of the mutant T cells was attributed to a perturbation of mitochondrial membrane potential (Foger et al., 2006), more recent studies have implicated an impaired Ca<sup>2+</sup> flux as the mechanism for most of the defects (Haraldsson et al., 2008; Mueller et al., 2008). In another study, severe depletion of mature T cells as the result of increased spontaneous death occurred after conditional deletion of an essential component of the COP9 signalosome, a negative regulator of the ubiquitin-protease system that selectively degrades key regulatory proteins of many cellular signaling pathways (Menon et al., 2007). Although the exact cause of T cell death in this study is not known, the remaining T cells comprised normal proportions of cells with a naive and memory phenotype, but displayed lower expression of CD127 (IL-7R) and were impaired in their responses to strong TCR stimulation.

With regard to transcription factors, Kruppel-like transcription factor KLF2, also known as LKLF, was implicated several years ago as one of the central regulators in maintaining quiescence and survival in mature T cells. Thus, KLF2 deficiency led to depletion of naive T cells in the secondary lymphoid organs, despite near-normal thymic development (Kuo et al., 1997). A recent study, however, revealed that the peripheral T cell lymphopenia seen in KLF2-deficient mice is the result of KLF2 being

essential for expression of several homing molecules, including sphingosine 1-phosphate receptor 1 (S1P<sub>1</sub>) and CD62L, which are required for thymocyte emigration and LN homing, respectively (Carlson et al., 2006). Moreover, KLF2 was also reported to repress expression of inflammatory chemokine receptors, such as CCR1 and CCR5, in naive T cells (Sebzda et al., 2008). Thus, in addition to their impaired ability to emigrate from the thymus and home to LN, post-thymic naive T cells from KLF2-deficient mice expressed the chemokine receptors normally found on activated T cells and thereby led to the cells being dispersed throughout various nonlymphoid tissues (Sebzda et al., 2008).

It is becoming increasingly clear that TCR signaling from contact with specific self-pMHC ligands is essential for survival of naive T cells, but the exact intracellular survival signaling pathways induced within T cells are just beginning to be deciphered.

### Naive T Cell Homeostasis and IL-7

The essential role of IL-7 as the major cytokine for naive T cell survival was discovered several years ago by the finding that blocking contact with IL-7, either by adoptive transfer of T cells into IL-7-deficient hosts or by injection of IL-7 mAb into normal mice, curtailed survival of naive T cells (Surh and Sprent, 2005); by the same token, overexpression of IL-7 increased the size of the naive T cell pool (Surh and Sprent, 2005). Hence, although IL-7 was initially defined on the basis of its nonredundant role in T cell (and B cell in the mouse) lymphopoiesis (von Freuden-Jeffry et al., 1995), it is now known to be an essential cytokine for both survival and homeostatic proliferation of naive and memory T cells (see below). For lymphopoiesis, IL-7 is produced locally by stromal and epithelial cells in the bone marrow and thymus. Similarly, IL-7 is thought to be produced locally in the secondary lymphoid organs (SLO) for mature T cell homeostasis and is likely to remain at the site of production, bound to the extracellular matrix, as described for other members of the  $\gamma_c$  cytokine family (Wrenshall and Platt, 1999). Much of the information on IL-7 production and localization has been obtained indirectly by examining mRNA expression and responses of T cells; the key problem here is that, thus far, *in vivo* amounts of IL-7 protein cannot be detected by immunohistochemistry. Nevertheless, it was initially suggested that local production of IL-7 within the secondary lymphoid organs was crucial for providing naive T cells with signals for survival and homeostatic proliferation (Dummer et al., 2001). More recently, a careful study of nonlymphoid cells isolated from the lymphoid organs has revealed that IL-7 is produced by a subset of fibroblastic reticular cells (FRC) situated in the T cell zones; FRC are wrapped around the conduits and produce a mixture of IL-7 and chemokines CCL19 and CCL21 (the ligands for CCR7), thereby attracting CCR7<sup>+</sup> T cells and providing these cells with signals for their survival (Link et al., 2007). At least *in vitro*, only FRC and not other types of stromal or hematopoietic cells isolated from LN were able to support survival of naive T cells through synthesis of IL-7 (Link et al., 2007).

Although synthesis of most  $\gamma_c$  cytokines can fluctuate, IL-7 is produced at a relatively fixed constitutive amount, independent of external stimuli. Nonetheless, T cell responses to IL-7 appear to be highly regulated through the modulation of the IL-7R $\alpha$  chain (CD127), which dimerizes with the  $\gamma_c$  chain to form the IL-7R (Leonard, 2001). CD127 is expressed on T cells at almost all

stages of development, starting with early CD4<sup>+</sup>CD8<sup>+</sup> “double-negative” (DN) progenitors in the thymus and extending to mature T cells in the peripheral lymphoid tissues. However, T cells downregulate CD127 whenever they undergo prominent expansion. Thus, DN thymocytes shut down expression of CD127 upon proliferation and differentiation into CD4<sup>+</sup>CD8<sup>+</sup> double-positive (DP) cells; most DP cells have a lifespan of 3–4 days, but the small fraction of these cells that undergoes positive selection re-expresses CD127 and differentiates into mature SP cells, which remain CD127<sup>+</sup> until they respond to foreign antigen (see below) (Mazzucchelli and Durum, 2007). Because forced transgenic expression of CD127 on DP cells causes increased death of DN cells (Munitic et al., 2004), it appears that DP cells downregulate CD127 in order to ensure continuous availability of IL-7 to DN and SP T cells. A similar IL-7-conserving scenario applies when naive T cells in the periphery are activated by foreign Ag to undergo massive expansion; here, strong TCR signaling downregulates CD127, such repression being sustained by newly synthesized IL-2 (Schluns et al., 2000; Xue et al., 2002). Remarkably, IL-7 conservation also applies at the level of naive T cells. Thus, naive T cells were found to downregulate CD127 after contact with IL-7 and reciprocally upregulate CD127 in the absence of IL-7, both under in vitro and in vivo conditions (Park et al., 2004). Such feedback control of CD127 expression is more than a simple process of ligand-induced receptor modulation, because it requires new protein synthesis. This finding helps to explain why normal naive T cell populations show a broad range of CD127 expression, thus ensuring that maximum numbers of T cells are maintained by exposure to a limiting low amount of IL-7 (Park et al., 2004). Consistent with this idea, forced constitutive high expression of transgenic CD127 on mature T cells caused a significant reduction in the overall size of the mature T cell pool (Park et al., 2004).

Because naive T cells continually recirculate between the secondary lymphoid organs and the blood, consumption of IL-7 is likely to occur during their passage through the lymphoid tissues, but not while in transit in the lymph and blood. Indeed, survival of naive T cells, especially CD4<sup>+</sup> T cells, was found to be impaired in thymectomized nuclear factor- $\kappa$ B inducing kinase (NIK<sup>aly/aly</sup>) mice deficient in SLO (Dai and Lakkis, 2001). The requirement for SLO appears to be because, as with IL-2 and IL-15 (Dubois et al., 2002; Wrenshall and Platt, 1999), IL-7 is probably displayed largely in cell-associated form at the site of production, bound to the extracellular matrix, instead of being distributed systemically in soluble form. This scenario, plus the fact that IL-7 binding induces downregulation of IL-7R, implies that naive T cells may need to be able to withstand repeated periods of loss of contact with IL-7. Consistent with this idea, T cell survival depends on autophagy, a highly conserved catabolic process of digestion of cytoplasmic constituents, which is essential for many cellular function, including cell survival during growth factor withdrawal (Lum et al., 2005). Hence, T cells lacking Ag5, a crucial autophagy gene, develop normally in the thymus but fail to survive and undergo spontaneous apoptosis after exit to the periphery (Pua et al., 2007).

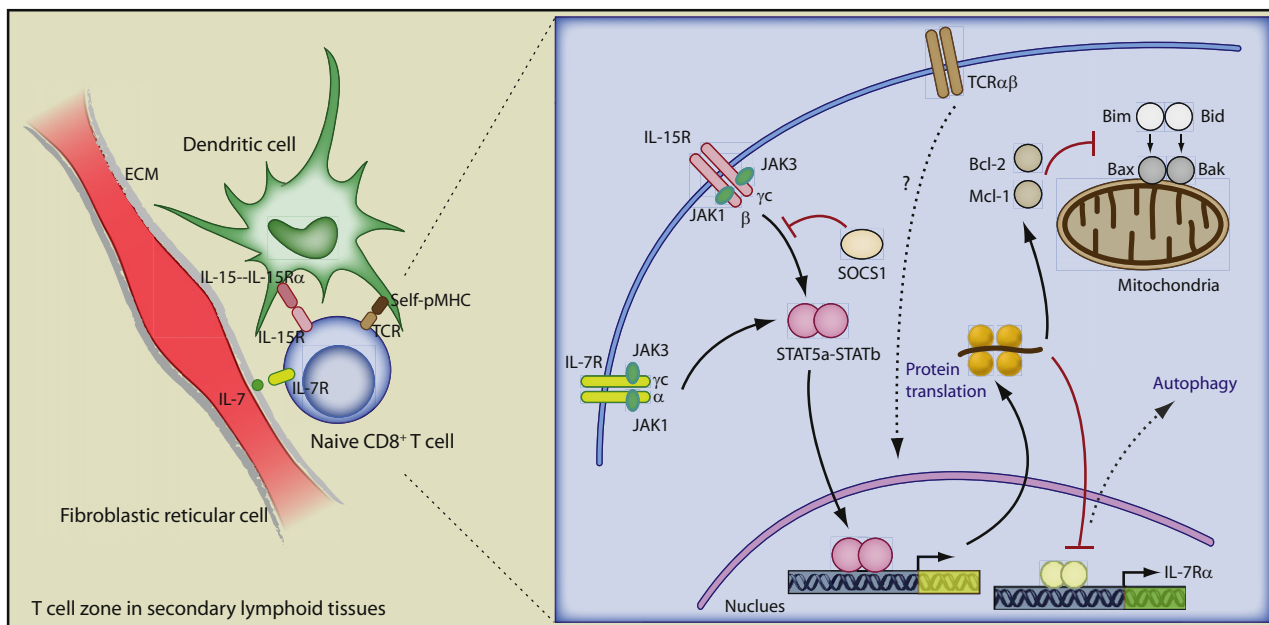
IL-7 is produced locally in the T cell areas of SLO by FRC and appears to be utilized intermittently by naive T cells because of IL-7-induced downregulation of IL-7R expression and from migration out of SLO during recirculation. Although such mecha-

nisms maximize the size of the naive T cell pool, naive T cells must withstand cycles of IL-7 deprivation.

### Naive T Cell Homeostasis and IL-7 Signaling

The survival signal induced by IL-7 binding is mediated through the activation of Jak1 and Jak3, which are bound to CD127 and  $\gamma_c$ , respectively (Figure 1). Such binding recruits and activates Stat5a/b, which results in the migration of activated Stat5a/b dimers to the nucleus to regulate gene transcription (Mazzucchelli and Durum, 2007). Accordingly, deletion of IL-7R,  $\gamma_c$ , or Jak3 each causes a similar syndrome of severe immunodeficiency as the result of defects in T cell development, both in humans and mice (Leonard, 2001). However, deficiency in either Stat5a or Stat5b alone does not severely impede lymphocyte development (Imada et al., 1998; Nakajima et al., 1997; Teglund et al., 1998). Nevertheless, combined deficiency of both Stat5a and Stat5b would be expected to lead to the same severe phenotype seen with deficiency in IL-7R,  $\gamma_c$ , or Jak3. Surprisingly, mutations at both Stat5a and Stat5b caused only a mild perturbation in lymphocyte development and survival (Teglund et al., 1998). More recent studies, however, revealed that this phenotype reflects expression of partially functional truncated Stat5a and Stat5b proteins; with complete deletion of the Stat5a and Stat5b locus, the T cell deficiency phenotype was as severe as in mice lacking IL-7R,  $\gamma_c$ , or Jak3 (Yao et al., 2006). In addition, deletion of Stat5a and Stat5b within mature T cells caused severe depletion of peripheral T cells, especially CD8<sup>+</sup> T cells, indicating the importance of Stat5a and Stat5b signaling for mature T cell survival (Yao et al., 2006).

IL-7 and related cytokines promote cell survival by preventing the mitochondrial pathway of apoptosis (Figure 1). In this respect, antiapoptotic Bcl-2 and Mcl-1 appear to play a dominant role because other antiapoptotic molecules are not expressed in naive T cells, although Bcl-X<sub>L</sub> is expressed by DP thymocytes and activated T cells. Bcl-2 and Mcl-1 are thought to mediate their function by directly regulating the activity of the death effectors Bax and Bak, which terminally induce apoptosis by causing the release of cytochrome c and other molecules from the mitochondria to initiate the activation of caspases (Khaled and Durum, 2002). In addition, Bcl-2 and Mcl-1 appear to block the family of BH-3-only Bcl-2-related molecules, including Bim and Bid, which directly activate Bax and Bak; Bcl-2 and Mcl-1 also interact with several other members of this family, including Bad and PUMA, which activate Bax and Bak indirectly by functioning as derepressors (Chipuk and Green, 2008). The role of Mcl-1 for naive T cell survival was demonstrated by the finding that deficiency of Mcl-1 during T cell development or specifically in mature T cells caused severe depletion of naive T cells (Opferman et al., 2003). The long-term crucial role of Bcl-2 on T cell survival was established by generating *Bcl2l11* (*Bim*)<sup>+/-</sup> *Bcl-2*<sup>-/-</sup> mice, thereby overcoming the problem of premature death seen with *Bcl-2*<sup>-/-</sup> mice. Significantly, despite their marked difference in lifespan, *Bcl-2*<sup>-/-</sup> and *Bcl2l11*<sup>+/-</sup> *Bcl-2*<sup>-/-</sup> mice both showed a severe reduction in total numbers of naive T cells, especially CD8<sup>+</sup> T cells, despite near-normal T cell development in the thymus (Bouillet et al., 2001; Veis et al., 1993; Wojciechowski et al., 2007). Strikingly, completely removal of Bcl2l11, as in *Bcl2l11*<sup>-/-</sup> *Bcl-2*<sup>-/-</sup> mice, largely restored naive T cell numbers, indicating



**Figure 1. Survival of Naive T Cells**

Survival of typical naive  $CD4^+$  and  $CD8^+$  T cells under normal physiological conditions requires signals from contact with self-peptide-MHC (pMHC) ligands on dendritic cells (DCs) and IL-7 on fibroblastic reticular cells (FRC), received in the T cell zone of the secondary lymphoid organs. Naive  $CD8^+$  T cells are also partly dependent on signals from contact with IL-15 expressed on DCs. Signaling through the cytokine receptors induces activation of the receptor-bound JAK1 and JAK3, which in turn activates STAT5a-b dimer. SOCS-1 negatively regulates the responsiveness of naive  $CD8^+$  T cells to IL-15 by neutralizing the activity of JAKs. STAT5a-b dimer then migrates into the nucleus, and together with signaling through TCR, initiates synthesis of various proteins, including Bcl-2 and Mcl-1 that prevent mitochondria-mediated apoptosis by blocking the BH-3-only Bim and Bid from activating Bax and Bak. New protein synthesis also leads to repression of IL-7R transcription, thereby reducing the IL-7R expression on the cell surface and rendering the cell to become temporarily starved of IL-7. During such IL-7-deprived state, cell survival appears to depend on intact autophagy.

that death is mediated primarily through Bcl2l11 (Wojciechowski et al., 2007).

IL-7 maintains survival of naive T cells by signaling through Jak3 and Stat5 and preventing mitochondrial pathway of apoptosis by inducing expression of Bcl-2 and Mcl-1.

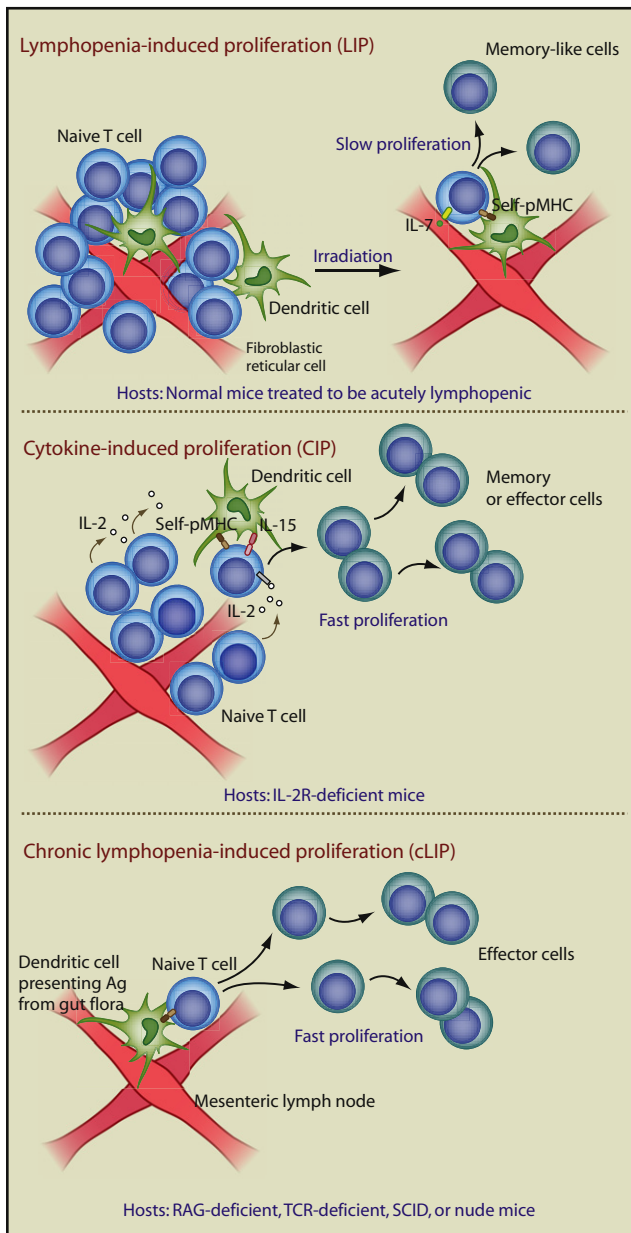
### Homeostatic Proliferation of Naive T Cells

Perhaps the strongest evidence for the existence of homeostatic mechanisms is the finding that mature T cells undergo spontaneous “homeostatic” proliferation in response to severe depletion of T cells. Indeed, it was the identification of the factors that drive homeostatic proliferation that led to the discovery of the key regulators of T cell survival. Thus, it was shown that naive T cells begin to proliferate in syngeneic lymphopenic hosts because of increased availability of specific self-pMHC ligands and/or IL-7, i.e., the same factors required for survival of naive T cells in interphase under normal nonlymphopenic conditions. Besides these canonical homeostatic ligands, it is now apparent that other signals can drive naive T cells to undergo proliferation in syngeneic hosts, sometimes at a rapid pace and even under T cell-replete conditions. As discussed below, the various types of homeostatic proliferation can be categorized according to the nature of the stimuli concerned (Figure 2).

### Homeostatic Proliferation Driven by Self-pMHC and IL-7

Homeostatic proliferation elicited by a combination of self-pMHC and IL-7 typically proceeds at a slow rate and is readily

observed for naive  $CD4^+$  and  $CD8^+$  T cells upon adoptive transfer into syngeneic normal hosts that have been made acutely lymphopenic, e.g., by irradiation (Ernst et al., 1999; Goldrath and Bevan, 1999; Schluns et al., 2000; Tan et al., 2001); in general,  $CD8^+$  cells proliferate more rapidly than do  $CD4^+$  cells. Because the dividing T cells gradually, and irreversibly, acquire the phenotype and characteristics of memory T cells, it has been suggested that lymphopenia-induced proliferation (LIP) is a more appropriate description of the phenomenon than homeostatic proliferation (Min et al., 2003). For normal polyclonal T cells, it is well established that LIP is severely diminished in the absence of either MHC or IL-7 (Ernst et al., 1999; Goldrath and Bevan, 1999; Schluns et al., 2000; Tan et al., 2001). The importance of self-pMHC ligands for LIP is also apparent from the finding that many lines of TCR transgenic T cells undergo LIP in the absence of cognate Ag (Ernst et al., 1999; Goldrath and Bevan, 1999; Schluns et al., 2000). Further evidence on this point came from studies with “single” pMHC complex mice, which demonstrated a close correlation between the ligands controlling LIP of mature naive T cells in the periphery (Ernst et al., 1999; Goldrath and Bevan, 1999; Viret et al., 1999). Collectively, these findings plus the fact that IL-7 concentration increase with T cell depletion (Fry and Mackall, 2001) indicate that LIP is driven by increased availability of IL-7, which amplifies the weak TCR signaling resulting from contact with self-pMHC ligands (Surh and Sprent, 2005).



**Figure 2. Different Types of Homeostatic Proliferation**

Three types of homeostatic proliferation are currently known to occur depending on the nature of the hosts.

Top: Lymphopenia-induced proliferation (LIP) is driven by overabundance of IL-7 and self-pMHC ligands when T cells are transferred into normal mice that have been rendered acutely lymphopenic by lympho-depleting procedure, such as exposure to irradiation or cytotoxic drugs. Naive T cells undergoing LIP divide at a slow rate and gradually acquire characteristics of memory T cells. Middle: Cytokine-induced proliferation (CIP) is driven by highly elevated amounts of IL-2 and/or IL-15; such conditions are apparent in IL-2R-deficient mice, i.e., in CD25-deficient, CD122-deficient, and CD132-deficient mice. Normal T cells proliferate very rapidly in these hosts and acquire characteristics of effector cells or central memory cells. Note that CD25-deficient and CD122-deficient mice display lymphadenopathy; hence, lymphopenia is not required for CIP. Bottom: Chronic lymphopenia-induced proliferation (cLIP) is driven by Ags from commensal microflora and is evident when T cells are transferred into congenital T cell-deficient hosts, such as RAG-deficient, SCID, nude, and TCR-deficient hosts. Naive T cells undergo a very rapid rate of proliferation and acquire characteristics of effector cells.

The overall combined strength of the signaling from the TCR and IL-7R appears to determine the relative propensity for naive T cells to undergo LIP. Accordingly, T cells with high-affinity TCR for self-pMHC ligands undergo faster rates of LIP than do low-affinity T cells (Kassiotis et al., 2003; Kieper et al., 2004). This notion is readily observed with TCR transgenic cells of high affinity such as OT-I; these cells are generated in large numbers and, on transfer, undergo a faster rate of LIP than cells of lower-affinity TCR, such as 2C or P14 (Kieper et al., 2004). Conversely, some very low-affinity TCR, such as HY (for CD8<sup>+</sup> cells) and OT-II (for CD4<sup>+</sup> cells), produce transgenic mice with only a tiny pool of peripheral T cells that are unable to undergo LIP (Ernst et al., 1999; Kieper et al., 2004).

In line with the importance of TCR signaling strength, molecules that intimately control signaling through the TCR can have a conspicuous influence on LIP and T cell homeostasis. Recently, three negative regulators of TCR signaling were found to modulate the rate of LIP, namely (1) CD223 (LAG-3), a CD4-like molecule that binds to MHC-II with high affinity (Workman and Vignali, 2005), (2) BTLA-4, a negative regulator of TCR signaling that binds to a TNF receptor family molecule HVEM (Krieg et al., 2007), and (3) SIT, a tyrosine phosphatase 2-binding transmembrane adaptor protein (Posevitz et al., 2008). Thus, both normal and TCR transgenic cells that lacked CD223, BTLA-4, or SIT underwent faster rates of LIP than did wild-type T cells (Krieg et al., 2007; Posevitz et al., 2008; Workman and Vignali, 2005). Indeed, even cells with low-affinity TCR, i.e., OT-II and HY cells, were able to undergo LIP in the absence of CD223 or SIT, respectively. There were also perturbations in the peripheral T cell pool size in these mutant mice, with increases of all T cell subsets in CD223-deficient mice, selective elevation of memory CD8<sup>+</sup> T cell numbers in BTLA-4-deficient mice, and a selective reduction of naive CD8<sup>+</sup> T cells in SIT-deficient mice. These findings may be the tip of the iceberg and it is highly likely that many different molecules influence T cell homeostasis through modulation of TCR signaling. Resolving this issue will take quite some time.

Although the covert TCR signaling required for LIP involves the coreceptor activity of CD4 and CD8, other cell-surface receptors do not appear to be essential. Thus, typical costimulatory molecules, such as CD28, CD40, and LFA-1, which are crucial for responses to foreign Ags, are dispensable for naive T cells undergoing LIP in response to self-pMHC ligands. One reported exception is CD24 (HSA), as indicated by the fact that CD24-deficient T cells are severely impaired in their ability to undergo LIP (Li et al., 2004). This finding is difficult to interpret because the function of CD24 for LIP is unknown and the counter receptor for CD24 has yet to be described. The role of CD24 is likely to be complex because wild-type donor T cells unexpectedly undergo massive proliferation upon adoptive transfer into irradiated CD24<sup>-</sup> mice (Li et al., 2006).

As mentioned earlier, low levels of IL-7 keep normal naive T cells alive in interphase by inducing the upregulation of antiapoptotic proteins such as Bcl-2 and Mcl-1. However, additional signals appear to be elicited by the elevated amounts of IL-7 that drive LIP. Thus, overexpression of Bcl-2 alone is not sufficient to compensate for the inability of naive T cells to undergo LIP in IL-7-deficient hosts (Tan et al., 2001). LIP requires intact signaling through the IL-7R $\alpha$  chain and is heavily dependent on the main signaling tyrosine residue of IL-7R $\alpha$ , Y449, which is

required for activation of STAT5 and Bcl-2 production (Jiang et al., 2004). Thus, mice expressing normal amounts of IL-7R $\alpha$  but with a mutated Y449F residue produced normal T cells, albeit in smaller numbers than that in normal mice, but the mutant T cells were virtually incapable of undergoing LIP (Osborne et al., 2007). The reduction in numbers of mature T cells in IL-7R $\alpha$ <sup>Y449F</sup> mice appeared to be due to impaired thymic development rather than from a defect in cell viability, although this was not measured directly, e.g., by analyzing the longevity of the T cell pool after thymectomy. Despite this caveat, these findings suggest that some survival signals can be delivered through IL-7R $\alpha$  outside of Y449, but such signaling is insufficient for LIP.

Further downstream, IL-7-driven entry into cell cycle appears to be partly a consequence of degradation of the cyclin-dependent kinase (cdk) inhibitor P27<sup>kip1</sup>, which binds and blocks cdk2 function, thus allowing activation of the kinase-cyclin complex and progression from G1 to the S phase of cell cycle (Sherr and Roberts, 1999). Accordingly, unlike normal T cells, P27<sup>kip1</sup>– T cells were able to undergo significant LIP in IL-7-deficient lymphopenic hosts (Li et al., 2003). However, LIP in these latter hosts was still considerably less than in normal lymphopenic hosts, suggesting the participation of other additional signals.

LIP of naive T cells in acutely lymphopenic hosts is driven by relatively high-affinity self-pMHC ligands and increased concentration of IL-7, but do not require typical costimulatory signals. The proliferation signals induced by IL-7 appears to be partly different from those that support cell survival.

### Homeostatic Proliferation Drive by Other Cytokines

Besides IL-7, it is now clear that homeostatic proliferation of naive T cells can be driven by elevated amounts of other  $\gamma_c$  cytokines, especially IL-2 and IL-15, and can occur even in the absence of lymphopenia. Finding a role for non-IL-7  $\gamma_c$  cytokines was unexpected because the absence of IL-2 or IL-15 in gene-deficient mice failed to have a notable effect on the rate of LIP in most types of lymphopenic hosts, including various strains of congenitally T-deficient mutant mice. However, a notable exception was observed when mice deficient in one of the three chains of the high-affinity IL-2R, IL-2R $\alpha\beta\gamma$ , were used as hosts without prior lympho-depletion. Thus, in CD25 (*Il2ra*)-deficient, CD122 (*Il2rb*)-deficient, or CD132 (*Il2rg*)-deficient hosts, normal donor naive T cells, including TCR transgenic cells, underwent a massive rate of proliferation, equivalent to T cell responses to foreign Ags, and the proliferating cells rapidly acquired the characteristics of effector cells or central (CD62L<sup>hi</sup>) memory cells (Cho et al., 2007; Ramsey et al., 2008). T cell proliferation in these hosts was skewed to CD8<sup>+</sup> T cells and was driven by extremely high amounts of IL-2 or a mixture of both IL-2 and IL-15. Importantly, the proliferation elicited by these cytokines was TCR dependent and required contact with self-pMHC ligands, either on host APCs or on adjacent T cells as the result of T-T interaction (Cho et al., 2007; Ramsey et al., 2008).

In line with the view that IL-2 and IL-15 differentially favor the generation of effector cells and central memory cells, respectively (Manjunath et al., 2001), the high amounts of IL-2 in *Il2ra*<sup>–/–</sup> and *Il2rb*<sup>–/–</sup> hosts appeared to skew differentiation of naive T cells into effector cells, whereas selective elevation of IL-15 over IL-2 in *Il2rg*<sup>–/–</sup> hosts elicited production of central memory cells (Cho et al., 2007; Ramsey et al., 2008). The high

amounts of IL-2 in *Il2ra*<sup>–/–</sup> and *Il2rb*<sup>–/–</sup> hosts appear to be the result of prominent IL-2 synthesis by the large numbers of activated T cells present in these mice combined with the absence of IL-2R<sup>+</sup> cells able to consume the cytokine. Why IL-15 is elevated in *Il2rg*<sup>–/–</sup> hosts is less clear. Thus, although decreased consumption of cytokines could be a contributing factor, depletion of all cells able to utilize IL-15 in congenitally T-deficient lymphopenic hosts failed to mimic the proliferation seen in *Il2rg*<sup>–/–</sup> hosts (Ramsey et al., 2008). Surprisingly, IL-7 did not appear to play any role because similar proliferation was seen in combined *Il2rg*<sup>–/–</sup> *Il7*<sup>–/–</sup> hosts (Ramsey et al., 2008). Collectively, these findings indicate that, despite expressing only relatively low amounts of IL-2R $\beta$ , the receptor for both IL-2 and IL-15, naive T cells are able to proliferate strongly in response to high concentrations of these cytokines, with the proviso that the cells also receive a TCR signal through recognition of self-pMHC ligands.

The proliferation of normal naive T cells in IL-2R-deficient mice can be viewed as another type of homeostatic proliferation because, as for LIP, it occurs without any intentional immunization and is driven by elevated amounts of cytokines plus TCR contact with self-pMHC ligands. It is notable that *Il2ra*<sup>–/–</sup> and *Il2rb*<sup>–/–</sup> hosts show marked lymphadenopathy, which indicates that homeostatic proliferation does not necessarily require lymphopenia. In fact, the “quality” of the homeostatic proliferative response is largely a reflection of the stimulatory capacity of the cytokines concerned. In this regard, IL-2 and IL-15 seem to transmit much stronger proliferative and differentiation signals than does IL-7. For this reason, production of IL-2 and IL-15 in vivo is probably tightly controlled in order to prevent unintended activation of bystander naive T cells during a strong immune response to pathogenic microbes. If it occurs, such bystander activation of naive T cells could be largely responsible for the progressive switch of these cells to T cells with a memory phenotype in advanced age.

Under normal physiological conditions, IL-2 does not appear to control homeostasis of T cells, with the notable exception of regulatory T (Treg) cells that are heavily dependent on IL-2. IL-15, on the other hand, does play an essential role in supporting homeostasis of naive CD8<sup>+</sup> T cells because IL-15-deficient mice possess about half the number of these cells as do wild-type mice (Berard et al., 2003; Kennedy et al., 2000). Additional evidence supporting this notion has recently emerged from studies with mice deficient in suppressor of cytokine signaling-1 (SOCS-1). SOCS-1 is one of eight members of the CIS-SOCS family of negative-feedback regulators of cytokine signal transduction that neutralize the activity of JAKs, and SOCS-1 is upregulated by many cytokines, including IL-2, -4, -7, and -15 (Yoshimura et al., 2007). Deficiency in SOCS-1 is known to greatly increase the sensitivity of DP thymocytes to IL-7 and IL-15 (Chong et al., 2003; Ramanathan et al., 2006). The striking finding, however, is that SOCS-1-deficient mature T cells display selective hyper-responsiveness to IL-15, though only for CD8<sup>+</sup> and not CD4<sup>+</sup> T cells (Davey et al., 2005; Ramanathan et al., 2006). Accordingly, in mice with SOCS-1 deficiency restricted to T cells or in SOCS-1-deficient mice that are additionally deficient in IFN- $\gamma$  (a prerequisite to circumvent early death), CD8<sup>+</sup> T cells consist predominantly of memory-phenotype (MP) cells and far outnumber CD4<sup>+</sup> T cells. The selective expansion of MP CD8<sup>+</sup> T cells in these mice appears to be driven largely by IL-15.

Thus, SOCS-1-deficient CD8<sup>+</sup> T cells, including TCR transgenic cells, were found to undergo homeostatic proliferation to self-pMHC ligands in T-sufficient normal or IL-7-deficient hosts, but not in IL-15-deficient hosts. Furthermore, the naive T cell pool in SOCS-1-deficient mice was restored to a near-normal composition and phenotype only in an IL-15-deficient, but not in an IL-7-deficient, background (Davey et al., 2005; Ramanathan et al., 2006).

The issue of why SOCS-1 regulates sensitivity to IL-7 only in immature but not mature T cells and whether a similar mechanism exists to control the responsiveness of naive T cells to IL-7 have yet to be answered. Furthermore, although naive CD4<sup>+</sup> and CD8<sup>+</sup> T cells both undergo homeostatic proliferation, the above findings with SOCS-1 plus the fact that CD8<sup>+</sup> T cells tend to undergo stronger homeostatic proliferation than CD4<sup>+</sup> T cells illustrate that subtle, but clear, differences exist between the two subsets of cells in the way homeostatic signals are transmitted and regulated intracellularly.

Naive T cells can be induced to undergo a very fast rate of homeostatic proliferation in response to very high levels of IL-2 and/or IL-15 and to differentiate into effector or memory T cells; this type of proliferation is now designated as cytokine-induced proliferation (CIP). Response of naive CD8<sup>+</sup> T cells to IL-15 under normal conditions is negatively regulated by SOCS-1.

#### Homeostatic Proliferation Driven by Commensal Ags

Although homeostatic proliferation is directed largely to self-pMHC ligands, it is now clear that a component of this response is induced by foreign Ags. In fact, it was initially argued that the bulk of LIP is driven by contact with environmental Ags (Mackall et al., 1997; Tanchot et al., 1997b). However, it is now apparent that the role of foreign antigens in LIP is quite variable and depends critically on the condition and immune status of the lymphopenic host (Kieper et al., 2005; Min et al., 2005). In particular, there are marked differences between acutely lymphopenic versus chronically lymphopenic hosts. Thus, when normal adult mice are made acutely lymphopenic by irradiation, LIP in these hosts is directed largely to self rather than foreign Ags; this also applies to irradiation of immunodeficient mice with a partial block in T cell development, e.g., in IL-7R-deficient mice. By contrast, in chronically lymphopenic hosts with a mutation that completely abolishes production of T cells, such as RAG-deficient, SCID, TCR-deficient, and nude hosts, a large component of LIP seems to be driven by foreign Ags. Proliferation in this situation is antigen specific because it is prominent only with polyclonal T cells. Thus, adoptive transfer of most lines of TCR transgenic T cells into RAG-deficient or SCID hosts results in only the typical slow IL-7-dependent form of LIP seen with transfer to acutely irradiated normal hosts (Kieper et al., 2005; Min et al., 2005). However, with transfer of polyclonal T cells to RAG-deficient or SCID hosts, the results are quite different. Here, a small fraction of the donor T cells proliferates at a very rapid rate; this response is independent of IL-7 and quickly overshadows the response of other cells undergoing slow LIP (Kieper et al., 2005; Min et al., 2005). By 1 week post-transfer, nearly all of the proliferating cells are the progeny of cells undergoing rapid proliferation.

Although the form of rapid T cell proliferation seen in chronically lymphopenic hosts is referred to by some workers as

“spontaneous” proliferation and hypothesized to reflect holes in the TCR repertoire (Min et al., 2005), the bulk of evidence strongly indicates that proliferation in this situation is directed largely to foreign Ags. Thus, unlike typical slow homeostatic proliferation, the rapid proliferation seen in RAG-deficient and SCID hosts was found to require costimulatory signals through CD28, and the expanding cells displayed many of the characteristics of T cells responding to foreign Ags, including rapid upregulation of acute activation markers and the acquisition of effector function (Hagen et al., 2004; Kieper et al., 2005; Min et al., 2005; Prlc et al., 2001). Rapid proliferation was dependent on the host being devoid of normal T cells, rather than from lymphopenia per se, and was prominent in RAG-deficient TCR transgenic hosts that possessed near normal numbers of a monoclonal population of T cells (Kieper et al., 2005; Min et al., 2005). Most importantly, the rapid T cell proliferation in SCID and RAG-deficient hosts was greatly reduced when the mice were raised in a germ-free environment (Kieper et al., 2005). This finding strongly suggests that the response is directed largely to the commensal microflora that reside in chronically immunodeficient hosts. This form of proliferation is quite different from typical LIP and can be referred to as “chronic lymphopenia-induced proliferation (cLIP)” directed to foreign Ags.

It is still unclear why Ags from commensal microflora cause cLIP only in chronically immunodeficient and not acutely lymphopenic hosts. In this regard, it has been known for many years that adoptive transfer of naive CD4<sup>+</sup> T cells to syngeneic RAG-deficient or SCID hosts induces the onset of chronic inflammatory bowel disease (IBD), presumably as a by-product of cLIP, and that onset of IBD can be prevented by cotransfer of Treg cells (Izcue et al., 2006). Although this finding has been interpreted as evidence that cLIP reflects the absence of Treg cells, recent studies have shown that Treg cells can only partially suppress cLIP, the main target of Treg cell suppression being the effector cells that have migrated from the lymphoid tissues into the intestines (Martin et al., 2004; Mottet et al., 2003). The alternative view, which we favor, is that the presence of normal T cells, perhaps a subset of memory cells, somehow sustains the integrity of the gut wall, thereby excluding entry of bacteria or their products. This protective mechanism is maintained, at least temporarily, after irradiation or in other forms of acute lymphopenia but fails in hosts with chronic T cell lymphopenia, thereby leading to entry of commensal Ags and onset of cLIP. The mechanisms involved in establishing and maintaining peaceful coexistence between the immune system and commensal microflora are likely to be complex and involve many layers of regulation by several types of cells, including T cells. cLIP may be a result of some dysregulation of the barriers that confine bacteria to the gut lumen. Here, local release of IL-22 by Th-17 cells could be important for protecting the gut lining (Aujla et al., 2008; Zheng et al., 2008).

The intense fast proliferation of naive T cells upon adoptive transfer into chronic lymphopenic hosts, now designated as cLIP, for chronic LIP, is primarily driven by Ags derived from commensal microflora.

#### Homeostasis of Memory T Cells

Although the survival of memory T cells was once thought to require contact with residual amounts of the priming Ag, it is now clear that the longevity and intermittent turnover of both memory








CD4<sup>+</sup> T and CD8<sup>+</sup> T cells is largely MHC independent and maintained through contact with a combination of IL-7 and IL-15. Knowledge of memory T cell homeostasis has arisen from studies on both naturally occurring memory-phenotype (MP) cells and Ag-specific (AgSp) memory T cells immunized with defined Ags. The factors regulating the homeostasis of MP and AgSp memory T cells are similar, but not identical (Figure 3).

### CD8<sup>+</sup> Memory T Cell Homeostasis

After the realization that MHC contact is irrelevant for survival of memory CD8<sup>+</sup> T cells, the finding that injection of adjuvants such as Poly IC or LPS without Ag caused a transient surge in the turnover rate of both Ag-specific and bystander memory CD8<sup>+</sup> T cells suggested that memory cells might be maintained largely by cytokines (Tough et al., 1996, 1997). Subsequent work revealed that adjuvants elicited the production of interferons (IFN), especially type I IFN (IFN-I), which in turn induced synthesis of IL-15 by a variety of non-T cells, including APC; IL-15 then acted directly on memory CD8<sup>+</sup> cells and boosted their basal rate of homeostatic proliferation (Tough et al., 1997; Zhang et al., 1998). The essential role of IL-15 in supporting survival and homeostatic proliferation of memory CD8<sup>+</sup> T cells was confirmed by studies with IL-15-deficient mice. Thus, these mice were found to lack the IL-15-responsive CD122<sup>hi</sup> subset of MP CD8<sup>+</sup> T cells (and NK cells), their residual MP CD8<sup>+</sup> T cells being CD122<sup>lo</sup> cells (Kennedy et al., 2000); moreover, MP CD8<sup>+</sup> T cells adoptively transferred into IL-15-deficient hosts failed to undergo homeostatic proliferation and died rapidly (Judge et al., 2002). In other studies, IL-15 transgenic mice were found to contain expanded numbers of MP CD8<sup>+</sup> T cells (Fehniger et al., 2001).

As mentioned earlier, the receptor for IL-15 (and IL-2) is composed of CD122 (IL-2R/IL-15R $\beta$ ) and CD132 ( $\gamma_c$ ); this  $\beta\gamma$  receptor is expressed at a high amount on memory CD8<sup>+</sup> T cells (and NK cells) and an intermediate amount on memory CD4<sup>+</sup> T and naive CD8<sup>+</sup> cells, but is undetectable on naive CD4<sup>+</sup> T cells (Zhang et al., 1998). Recent work showed that expression of CD122 is regulated by two related T-box transcription factors, T-bet and Eomesodermin (Eomes), which are upregulated on naive CD8<sup>+</sup> T cells upon activation and differentiation in effector and memory CD8<sup>+</sup> T cells (Intlekofer et al., 2005). Accordingly, mutations in both T-bet and Eomes resulted in severe depletion of MP CD8<sup>+</sup> T cells and NK cells, similar to the defect seen in IL-15 mice (Intlekofer et al., 2005).

Unlike other  $\gamma_c$  cytokines, IL-15 is unique in being presented on the cell surface tightly bound to the IL-15R $\alpha$  chain (Ma et al., 2006). Indeed, measurements have shown that the affinity of IL-15R $\alpha$  for IL-15 is three orders of magnitude stronger than the affinity of IL-2R $\alpha$  for IL-2 and also for CD122-CD132 binding of IL-15. In line with IL-15 being a cell-associated cytokine, soluble IL-15 is virtually undetectable in plasma (Bulanova et al., 2007). Cellular presentation of IL-15 was first directly demonstrated with human cell lines and then confirmed in the mouse by the finding that IL-15 activity in vivo required synthesis and expression of IL-15 and IL-15R $\alpha$  by the same cell (Burkett et al., 2004; Dubois et al., 2002; Sandau et al., 2004). This finding also explained the paradoxical observations that IL-15R $\alpha$ -deficient mice have the same defects as did IL-15-deficient mice and that injection of Poly IC could not induce bystander prolifer-

|   | Stimulation               | Phenotype<br>(all CD44 <sup>hi</sup> )    | Turnover<br>rate  | Survival;<br>homeostatic<br>proliferation |
|---|---------------------------|---|-------------------|---|
|    | Infectious<br>pathogens   | CD22 <sup>hi</sup><br>CD127 <sup>hi</sup> | Slow              | IL-7; IL-15                               |
|    | Protein Ags<br>+ adjuvant | CD22 <sup>hi</sup><br>CD127 <sup>hi</sup> | Slow              | IL-15; IL-15<br>(or high IL-7)            |
|    | Self-Ags                  | CD22 <sup>hi</sup><br>CD127 <sup>hi</sup> | Slow              | IL-15; IL-15<br>(or high IL-7)            |
|    | Commensal<br>or self-Ags  | CD22 <sup>lo</sup><br>CD127 <sup>lo</sup> | Moderate<br>-fast | MHC I; MHC I                              |
|   | Infectious<br>pathogens   | CD22 <sup>lo</sup><br>CD127 <sup>hi</sup> | Slow              | IL-7 + IL-15;<br>IL-7 + IL-15             |
|  | Commensal<br>or self-Ags  | CD22 <sup>lo</sup><br>CD127 <sup>hi</sup> | Slow              | IL-7 + IL-15;<br>IL-7 + IL-15             |
|  | Commensal<br>or self-Ags  | CD22 <sup>lo</sup><br>CD127 <sup>hi</sup> | Fast              | IL-7 + IL-15;<br>IL-7 + IL-15<br>+ MHC II |

**Figure 3. Memory T Cell Subsets with Variable Homeostatic Requirements**

Ag-specific (AgSp) memory and memory phenotype (MP) T cells arise in response to foreign, commensal, or self-antigens. Many pathogens that induce acute infection will induce bone fide memory T cells that are dependent on IL-7 and IL-15 for their survival and basal homeostatic proliferation. Memory cells generated from protein Ags, commensal, or self-Ags display slightly different requirements for their survival and homeostatic proliferation. MP cells whose homeostatic proliferation is driven by MHC undergo a considerably faster rate of turnover than MP cells dependent only on cytokines.

ation of MP CD8<sup>+</sup> cells transferred into IL-15R $\alpha$ -deficient hosts (Lodolce et al., 1998, 2001). IL-15R $\alpha$  is expressed on T cells but its function on these cells is obscure because IL-15R $\alpha$ -deficient CD8<sup>+</sup> T cells appear to have the same reactivity to IL-15 as WT cells (Burkett et al., 2003).

Because the CD122-CD132 ( $\beta\gamma$ ) receptor binds IL-2 as well as IL-15, it may seem surprising that IL-15-deficient mice are virtually devoid of CD122<sup>hi</sup> cells. Thus, why don't the background amounts of IL-2 in IL-15-deficient mice compensate for the lack of IL-15? A clue to this puzzle came from the observation

that the absence of CD122<sup>hi</sup> cells in IL-15-deficient mice could be overcome by injection of anti-IL-2 mAb (Kamimura et al., 2004). Though not understood at the time, this finding is now known to reflect the capacity of mAb binding to boost the activity of endogenous IL-2 activity in vivo (Boyman et al., 2006b). Hence, normal amounts of IL-2 in vivo, though adequate to stimulate CD25<sup>+</sup> Treg cells, are simply too low to be seen by cells with the weak IL-2R $\beta\gamma$ . It is worth noting that, in marked contrast to IL-15-deficient mice, large numbers of CD122<sup>hi</sup> cells are generated in SOCS-1 and IL-15 double-deficient mice (Ramanathan et al., 2006), suggesting that CD122<sup>hi</sup> cells may acquire sensitivity to endogenous IL-2 in the absence of SOCS-1.

Memory CD8<sup>+</sup> T cells express high amounts of IL-7R, and homeostasis of these cells is dependent on IL-7 as well as IL-15. Although background amounts of IL-7 are insufficient to support generation and survival of MP CD8<sup>+</sup> T cells in IL-15-deficient mice, the absence of these cells can be overcome by overexpressing IL-7. Thus, normal numbers of MP CD8<sup>+</sup> T cells were found in IL-15-deficient mice crossed to an IL-7 transgenic (Tg) background (Kieper et al., 2002). Likewise, elevated amounts of IL-7 in lymphopenic hosts induced LIP of MP CD8<sup>+</sup> T cells in the absence of IL-15 (Goldrath et al., 2002; Tan et al., 2002). Interestingly, AgSp memory CD8<sup>+</sup> T cells are even more dependent on IL-7 for survival than MP CD8<sup>+</sup> T cells. Thus, AgSp memory CD8<sup>+</sup> T cells developed in IL-15-deficient mice after infection with pathogens, but these cells failed to undergo basal homeostatic proliferation and gradually disappeared (Becker et al., 2002). Such findings have led to the current paradigm that AgSp memory CD8<sup>+</sup> T cells require contact with both IL-7 and IL-15 for their long-term survival, whereas basal homeostatic proliferation of these cells is controlled largely by IL-15. This model was recently confirmed in three studies that utilized genetic approaches to selectively abolish IL-7R signaling in mature CD8<sup>+</sup> T cells or replace wild-type IL-7R with the Y449F mutant IL-7R that cannot transmit signals to activate STAT5 and induce Bcl-2 production (Buentke et al., 2006; Carrio et al., 2007; Osborne et al., 2007). The notable finding was that, although IL-7R mutant naive T cells were able to differentiate into AgSp memory cells and respond to IL-15 by undergoing a normal rate of basal turnover, these cells nonetheless gradually disappeared, presumably because of inadequate IL-7 signaling. Significantly, overexpression of Bcl-2 rescued the slow death of IL-7R mutant memory CD8<sup>+</sup> T cells, indicating that the primary function of IL-7 is to upregulate Bcl-2 via STAT5 (Carrio et al., 2007; Osborne et al., 2007).

Homeostasis of memory CD8<sup>+</sup> T cells is regulated by a combination of IL-7 and IL-15, with IL-7 primarily supporting cell viability and IL-15 inducing basal homeostatic proliferation. This applies to AgSp memory CD8<sup>+</sup> T cells whereas the bulk of MP CD8<sup>+</sup> T cells is dependent only on IL-15 for their homeostasis.

### Heterogeneity in CD8<sup>+</sup> Memory T Cell Homeostasis

Why AgSp memory CD8<sup>+</sup> T cells are more dependent on IL-7 than MP CD8<sup>+</sup> T cells is unclear, but this difference could be a consequence of the conditions encountered during priming, in particular the overall “strength” and duration of priming. In this respect, the strong dependence of AgSp memory CD8<sup>+</sup> T cells on IL-7 rather than IL-15 for their long-term survival was found to be more pronounced for cells primed by infectious

agents (which led to prolonged responses) than by injection of a protein Ag plus purified adjuvant; for the latter, AgSp memory CD8<sup>+</sup> cells were as acutely dependent on IL-15 as MP CD8<sup>+</sup> T cells (Burkett et al., 2003). Although MP CD8<sup>+</sup> T cells are often considered as surrogates for AgSp memory cells, the origin of MP CD8<sup>+</sup> T cells has yet to be clearly defined. Although many MP CD8<sup>+</sup> T cells presumably emerge from immune responses to various environmental Ags, it is striking that near-normal numbers of these cells are found in germ-free, and even antigen-free, mice (Pereira et al., 1986; Vos et al., 1992). Hence, many MP T cells may be the progeny of cells undergoing homeostatic responses to self-pMHC ligands. Although the precise conditions required for “priming” T cells to self-Ags are unknown, these responses are presumably quite weak and may be of limited duration, i.e., as for cells responding to soluble protein Ags (see above). These conditions may preferentially generate IL-15-dependent memory cells.

Despite the differences in their mode of development, MP cells generated after LIP are strikingly similar to AgSp memory cells in their ability to undergo vigorous secondary responses and display effector function (Hamilton et al., 2006). Notably, both types of memory cells are dependent on “help” from CD4 T cells during priming to undergo optimal differentiation into protective memory cells (Bevan, 2004). Thus, as with AgSp memory CD8<sup>+</sup> T cells, TCR transgenic MP memory cells generated through LIP in the absence of CD4<sup>+</sup> T cells were functionally impaired and conferred no better protection from infection against pathogens than did naive T cells (Hamilton et al., 2006). This functional deficiency was found to be dependent on TNF-related apoptosis-inducing ligand (TRAIL), which is also reported to be the case for “unhelped” AgSp memory T cells (Janssen et al., 2005). In addition to aiding differentiation of naive CD8<sup>+</sup> T cells during their initial activation, the continual presence of CD4<sup>+</sup> T cells is also essential for memory CD8<sup>+</sup> T cells to display optimal effector function and long-term survival. Thus, wild-type AgSp memory CD8<sup>+</sup> T cells transferred into hosts deficient in CD4<sup>+</sup> T cells displayed impaired effector function upon restimulation and gradually disappeared (Sun et al., 2004). The precise cause of the shortened lifespan of unhelped memory CD8<sup>+</sup> T cells has yet to be resolved; the unhelped cells show downregulation of IL-7R $\alpha$  and CD122, though whether this is cause or effect is unclear (Sun et al., 2004).

For MP CD8<sup>+</sup> cells, most of these cells form a relatively homogeneous population of CD122<sup>hi</sup> resting cells with only occasional entry into cell division. In addition, however, ~30% of CD44<sup>hi</sup> MP CD8<sup>+</sup> cells have a rapid rate of turnover and display a semiactivated phenotype (CD62L<sup>lo</sup>, CD69<sup>hi</sup>) with low expression amounts of IL-7R and IL-15R (CD122<sup>lo</sup>). In marked contrast to the CD122<sup>hi</sup> subset, CD122<sup>lo</sup> MP CD8<sup>+</sup> T cells are MHC-I dependent but IL-15 independent; thus, these cells cease to proliferate and disappear rapidly upon adoptive transfer into MHC-I<sup>−</sup> hosts, implying that the cells are engaged in TCR-driven responses to MHC ligands (Boyman et al., 2006a). In this respect, the CD122<sup>lo</sup> MP CD8<sup>+</sup> T cells closely resemble the memory-like CD8<sup>+</sup> T cells that persist in hosts with a chronic viral infection. In this situation, constant contact with Ag keeps the responding cells in a semiactivated state, and the cells become dependent on TCR signaling instead of cytokines for their survival (Shin et al., 2007). The important question of whether CD122<sup>lo</sup> MP

CD8<sup>+</sup> T cells arise and persist through contact with self versus foreign Ags has yet to be resolved.

As for MP cells, AgSp memory cells are a heterogeneous population. Thus, memory CD8<sup>+</sup> T cells generated after an acute infection can be divided into two different subsets according to their surface markers and migratory capabilities. These two populations of cells appear to be regulated by somewhat different homeostatic mechanisms. In particular, CCR7<sup>+</sup> CD62L<sup>hi</sup> central memory cells (T<sub>CM</sub>) are largely confined to the secondary lymphoid tissues, whereas CCR7<sup>−</sup> CD62L<sup>lo</sup> effector memory cells (T<sub>EM</sub>) reside within nonlymphoid tissues as well as the spleen. Also, despite the fact that the two subsets display similar amounts of CD122, central memory CD8<sup>+</sup> cells display a faster rate of basal homeostatic proliferation than the effector memory subset (Wherry et al., 2003). In addition, a recent study suggests that homeostatic control of these two subsets is strikingly different after secondary contact with Ag. This study confirmed previous findings (Selin and Welsh, 2004) that the overall pool size of T<sub>CM</sub> is tightly regulated during secondary responses. In marked contrast, however, the population of T<sub>EM</sub> was found to expand enormously with repeated immunizations, especially with heterologous prime-boost immunizations designed to induce selective expansion of CD8<sup>+</sup> T cells to one Ag (Vezys et al., 2008). The mechanism that controls survival of large numbers of T<sub>EM</sub> but not T<sub>CM</sub> was not elucidated.

MP CD8<sup>+</sup> T cells generated from naive T cells though LIP are similar to AgSp memory CD8<sup>+</sup> T cells in terms of their functional capacity even though their homeostatic requirements are different. Other subsets of memory CD8<sup>+</sup> T cells with differential homeostatic requirements are CD122<sup>lo</sup> MP CD8<sup>+</sup> T cells, which are primarily dependent on MHC-I, and AgSp effector memory CD8<sup>+</sup> T cells, which can persist in extremely large numbers.

### CD4<sup>+</sup> Memory T Cell Homeostasis

As with memory CD8<sup>+</sup> T cells, TCR signaling from contact with MHC molecules is considered to be largely irrelevant for homeostasis of typical AgSp memory CD4<sup>+</sup> T cells. Thus, recent studies have shown that these cells do not require contact with MHC class II (MHC-II) molecules in order to stay alive and undergo homeostatic proliferation (Polic et al., 2001; Swain et al., 1999). There is one report that persistent contact with MHC-II molecules is needed to ensure that AgSp CD4<sup>+</sup> T cells display a full range of effector functions upon restimulation (Kassiotis et al., 2002). However, the physiological relevance of this finding is questionable because AgSp CD4<sup>+</sup> T cells were generated and studied in  $\gamma_c$ -deficient hosts, which harbor unphysiologically high amounts of IL-2 and IL-15; these cytokines are now known to induce strong activation of CD4<sup>+</sup> and CD8<sup>+</sup> T cells and this response can be further augmented by contact with self-MHC molecules (Cho et al., 2007; Ramsey et al., 2008).

The situation with MP CD4<sup>+</sup> cells is less clear. Thus, although AgSp and MP CD4<sup>+</sup> cells are tacitly assumed to be equivalent, these two cell types do not display the same homeostatic requirements. In particular, MHC-II molecules clearly do have a role in homeostasis of MP CD4<sup>+</sup> T cells, though only for homeostatic proliferation and not for long-term survival of these cells. In this respect, ablation of TCR expression or its signaling capacity specifically in mature T cells in normal mice substantially reduced the background turnover rate of MP CD4<sup>+</sup> T cells, but

not their overall pool size (Polic et al., 2001; Seddon et al., 2003). With regard to turnover, it is notable that, at a population level, MP CD4<sup>+</sup> T cells undergo a 2- to 3-fold faster rate of basal homeostatic proliferation than do AgSp memory CD4<sup>+</sup> T cells (Tough and Sprent, 1994). Much of this difference, however, is due to very rapid proliferation by a small subset of MP CD4<sup>+</sup> T cells (Purton et al., 2007; Robertson et al., 2006; Tan et al., 2002). These fast-dividing cells are readily observed in adoptive transfer experiments in lymphopenic hosts. Here, it was initially thought that the rapidly dividing cells did not require MHC-II contact because the cells proliferated in H2-A $\beta$ -deficient hosts (Tan et al., 2002). However, it now appears that these mice contain residual hybrid MHC-II molecules, namely heterodimeric H2-A $\alpha$ E $\beta$  molecules (Martin et al., 2003; Purton et al., 2007; Robertson et al., 2006). These MHC-II ligands appear functionally important because MP CD4<sup>+</sup> cells do not undergo rapid proliferation when transferred to mice that lack all MHC-II ligands, i.e., both H2-A $\alpha$  $\beta$  and H2-E $\alpha$  $\beta$  heterodimers or both H2-A $\beta$  and the invariant chain (Purton et al., 2007; Robertson et al., 2006). In the latter hosts, the donor MP CD4<sup>+</sup> cells undergo the same form of slow homeostatic proliferation as do AgSp memory CD4<sup>+</sup> T cells (Purton et al., 2007; Robertson et al., 2006). These findings imply that MP CD4<sup>+</sup> T cells are a heterogeneous population and contain a fraction of cells that is engaged in chronic rapid proliferative responses to MHC-II ligands, i.e., as for the component of MHC-I-dependent MP CD8<sup>+</sup> T cells (Boyman et al., 2006a). Whether the cells are responding to foreign antigens, e.g., commensal bacteria, or self-Ags is unknown and will require careful analysis of germ-free and antigen-free mice.

Although memory CD4<sup>+</sup> T cells were initially considered to be independent of  $\gamma_c$  cytokines, normal homeostasis of these cells is now known to require both IL-7 and IL-15 (Lantz et al., 2000; Tan et al., 2002). Although IL-7R is expressed at high amounts on memory CD4<sup>+</sup> T cells, these cells have only low amounts of CD122, equivalent to the amounts on naive CD8<sup>+</sup> T cells. A role for IL-7 became clear with the finding that both MP and AgSp memory CD4<sup>+</sup> T cells are heavily dependent on IL-7 for their survival, even in the presence of MHC-II molecules (Kon-drack et al., 2003; Lenz et al., 2004; Purton et al., 2007; Seddon and Zamoyska, 2002a). IL-7 was also found to be essential for AgSp memory CD4<sup>+</sup> T cells to undergo homeostatic proliferation, especially under lymphopenic conditions (Lenz et al., 2004; Purton et al., 2007). A role for IL-15 was not expected; IL-15-deficient mice possess normal numbers of MP CD4<sup>+</sup> T cells. Nonetheless, recent studies revealed that AgSp memory CD4<sup>+</sup> T cells require contact with both IL-15 and IL-7 to undergo basal homeostatic proliferation and also to survive for prolonged periods under T cell-replete conditions (Lenz et al., 2004; Purton et al., 2007). In lymphopenic conditions, however, IL-15 has only a minor role; thus, as for naive CD4<sup>+</sup> cells, LIP and differentiation into MP cells requires only IL-7 and not IL-15 (Purton et al., 2007).

Collectively, these findings indicate that memory CD4<sup>+</sup> T cells are broadly similar to memory CD8<sup>+</sup> T cells in needing a combination of IL-7 and IL-15 for their homeostasis. The one minor difference is that basal homeostatic proliferation of memory cells requires both IL-7 and IL-15 for CD4<sup>+</sup> T cells but only IL-15 for CD8<sup>+</sup> T cells; for CD4<sup>+</sup> memory cells, the less conspicuous role of IL-15 correlates with lower expression of CD122 than on memory CD8<sup>+</sup> cells.

For AgSp memory CD8<sup>+</sup> cells, it was mentioned earlier that these cells survive almost indefinitely in constant numbers. By contrast, numbers of memory CD4<sup>+</sup> cell numbers gradually decline with time (Homann et al., 2001). The reason for this difference is not fully understood, but could be partly a result of the inability of CD122<sup>lo</sup> AgSp memory CD4<sup>+</sup> T cells to compete for IL-15 in the presence of CD122<sup>hi</sup> CD8<sup>+</sup> T cells and NK cells. In support of this notion, the basal homeostatic proliferation rate of AgSp memory CD4<sup>+</sup> T cells increased substantially after removal of CD8<sup>+</sup> T cells and NK cells (Purton et al., 2007). Another factor could be that the AgSp memory CD4<sup>+</sup> T cell pool may be continuously selected over time to be enriched for cells with high functional avidity against the cognate Ag (Williams et al., 2008). In this respect, a recent study showed the expected slow decay in AgSp memory CD4<sup>+</sup> T cell numbers when Ag-specific cell numbers were measured with a high dose of Ag, which detects both high- and low-TCR-avidity cells. By contrast, analysis with a low dose of Ag revealed that high-avidity memory cells did not decline with time (Williams et al., 2008). How such selection was achieved in this study is unclear, but could be a reflection of the strength of the initial TCR signaling that the naive precursor cells encountered during the primary response. In support of this notion, AgSp memory CD4<sup>+</sup> T cells generated from an unphysiologically high precursor frequency of naive CD4<sup>+</sup> T cells displayed a much shorter lifespan than memory CD4<sup>+</sup> T cells generated from a normal low frequency of precursor cells, presumably because of reduced signaling resulting from clonal competition (Hataye et al., 2006). Because naive CD4<sup>+</sup> cells require a prolonged period of stimulation to undergo efficient differentiation into memory cells (Williams et al., 2008), the overall strength of signaling encountered by the responding cells may vary for each cell and depend on the avidity of TCR/Ag interaction. Hence, it is possible that high-avidity cells may establish a more sensitive “wiring” of the receptors for IL-7 and IL-15 than cells of lower avidity.

Homeostasis of memory CD4<sup>+</sup> T cells is largely regulated by IL-7 and IL-15, similar to memory CD8<sup>+</sup> T cells, although IL-7 appears to have a bigger role for memory CD4<sup>+</sup> T cells than for CD8<sup>+</sup> T cells.

### Concluding Comments

As discussed above, T cell production and survival are tightly constrained by competition for cytokines and self-pMHC ligands. Such competition allows the size of the T cell pool to increase progressively during young life and then remain relatively constant throughout adult life. The homeostatic mechanisms that shape the size and composition of the T cell pool are still poorly understood, and it is notable that total T cell numbers are maintained despite a gradual transition of naive T cells into memory cells with age. Because this switch in phenotype is also observed in germ-free conditions, the stimulus for this transition presumably involves self-Ags as well as foreign Ags. Although the precise cause of this switch is unclear, it is well documented that T cells are TCR dependent for their survival and that immature T cells are positively selected for covert reactivity to self-pMHC ligands during their formation in the thymus. Because differentiation into mature T cells leads to upregulation of TCR and various costimulation and adhesion molecules, T cell maturation would be expected to augment TCR reactivity to self-

ligands, thereby causing the cells to display overt autoreactivity. The fact that mature T cells usually remain self-tolerant is partly attributable to the action of Treg cells, but also reflects a process of “tuning” whereby TCR responsiveness to self-ligands is decreased before mature T cells are released from the thymus. TCR tuning is delicately balanced so as to allow naive T cells to receive weak signals that are just sufficient to promote survival but not to push the cells into division. The molecular control of TCR tuning is highly complex and involves upregulation or maintenance of a variety of negative regulators discussed earlier, including CD223, BTLA-4, SIT, and SOCS-1, as well as CD5 (Tarakhovsky et al., 1995) and miR-181a (Li et al., 2007). Modulation of these regulators might be involved in promoting the transition of naive T cells into memory cells, i.e., by boosting TCR signaling by self-ligands, but direct evidence on this interesting question is sparse. As discussed earlier, naive T cells can be induced to divide by exposure to high concentrations of cytokines, but whether these “anti-self” responses involve modulation of the above negative regulators is unknown.

Conceivably, another layer of TCR tuning may occur after the switch of naive T cells into memory cells. Thus, both for MP and AgSp memory cells, the survival of these cells is largely MHC independent. This finding implies that, relative to naive cells, memory cells have undergone a further process of TCR desensitization, causing the cells to ignore self-MHC ligands and rely entirely on contact with cytokines for their survival. How this process of apparent decreased reactivity to self-Ags is controlled despite retention of strong responsiveness to foreign Ags is still largely obscure.

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