Published in final edited form as:

Trends Immunol. 2012 May ; 33(5): 224–230. doi:10.1016/j.it.2012.01.007.

CD8 T cell quiescence revisited

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Abstract

Naïve T cells are typically considered to be in a default state of quiescence, while memory T cells undergo basal proliferation and quickly exhibit effector responses when stimulated. Over the last few years, however, a more complex picture has emerged, with evidence that naïve T cell quiescence is actively enforced, and that heterogeneity among naïve T cells influences their capacity to escape quiescence in response to homeostatic cues. Furthermore, the active state of memory T cells may also be instructed, requiring contact with dendritic cells to avoid reversion to quiescence. Here we discuss these new findings and propose that there is much more flexibility in the quiescent state of naïve and memory T cells than previously thought.

Creating and Maintaining an Effective CD8+ T cell Pool

T cells develop in the thymus and are released into the periphery as mature, naïve cells. Circulation through secondary lymphoid organs ensues as naïve cells search for specific antigens presented in the context of appropriate MHC molecules. The number of naïve CD8 T cell precursors which can recognize a given foreign peptide/MHC ligand has been determined experimentally to be in the range of ~100 to ~1000 cells per mouse [1, 2]. Therefore, upon recognition of ligand and activation, a robust proliferation program must be initiated to stimulate a few CD8+ T cell clones to generate hundreds of thousands of effector cells within a few days. Initiation and progression of the cell cycle is critically regulated by numerous extracellular factors that culminate in the activation of cyclins and cyclin-dependent kinases within the responding cell [3, 4]. The sizeable expansion of the T cell pool is followed by a contraction phase in which most effector cells die by apoptosis. The remaining cells form the memory cell pool, which is heterogeneous in make up, and phenotypically and functionally distinct from their naïve counterparts [5]. Unlike quiescent naïve cells, memory cells undergo slow, basal turnover for months to years [6], maintaining low numbers of antigen-experienced cells in the event that a second encounter with antigen occurs.

Overall, the T cell compartment must constantly achieve a balancing act of cell survival without inappropriate cell activation, yet also maintain the capability to rapidly enter and progress through cell cycle when increased numbers of cells are needed to replenish the T cell pool or participate in an immune response. This article will discuss recent work on the factors influencing the quiescence of T cells and conditions that support cell cycle progression, highlighting the unique needs of the naïve and memory cell pool. As we will discuss, new reports have identified novel factors involved in enforcing naïve T cell

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quiescence and driving the more active state of memory T cells. Intriguingly, one conclusion of these recent studies is that the separation of the naïve and memory T cell pools may not be as rigid as previously thought, and that cells may change in their properties depending on prevailing homeostatic cues (Figure 1).

Naïve T cell Survival and Quiescence

Mature, naïve CD8⁺ T cells are thought to have relatively low basal metabolic activity and to be maintained in interphase for months to years while sustaining their naïve differentiation state [7, 8]. Maintenance of naïve T cells involves sustained contact with MHC molecules presenting self-peptides and IL-7 [6, 9], as evidenced by the decline in naïve T cells deprived of contact with suitable MHC ligands (or interruption of TCR signals) and loss or blockade of IL-7R [6, 10–15]. In addition to maintaining survival, homeostatic cues may regulate the function of naïve T cells. While there is still controversy about whether encounter with self peptide/MHC enhances or diminishes reactivity to foreign peptide/MHC [9], steady state encounter with dendritic cells appears essential for maintaining naïve CD4 and CD8 T cell function, since deprivation of these encounters causes rapid loss of functional sensitivity [16].

The TCR and IL-7R are also involved in thymic development, and it is appealing to conclude that engagement of these receptors in naïve T cells helps sustain the signals induced during successful thymic selection, leading to maintenance of the resting naïve T cell pool. The fact that such signals led to expression of genes responsible for cell survival (such as IL-7-induced Bcl-2) fits with the idea that IL-7R and low grade TCR signals are important for keeping naïve T cells alive, yet in a dormant, non-dividing (i.e. quiescent) state. However, it has become clear that there is more complexity in the maintenance of naïve T cells than initially thought (Box 1).

BOX 1

What is quiescence anyway?

Quiescent

A. adj. 1. a. In a state or condition of quietness; motionless; inactive; dormant. (Oxford English Dictionary)

While “quiescent” is often used in cellular biology to specify cells that are in the G₀ phase of cell division, a broader definition would suggest cells at rest. Loss of quiescence would therefore include a variety of changes, including both proliferation and differentiation. The naïve T cell pool has long been considered a prototype of resting cells, lying in a default dormant state while awaiting the TCR signals that ignite its function. However, as we will discuss, recent data suggest quiescence is an actively enforced condition, and there is heterogeneity in the naïve T cell pool for their capacity to proliferate and differentiate in response to homeostatic cues. In addition, it is becoming clear that the more active state of memory T cells is not a default property either, but requires regular reinforcement. Hence, it is time to question models proposing a rigid distinction between the quiescent state of naïve and memory T cells, and to appreciate that the boundary distinguishing these populations may be more porous than previously thought.

Regulation of naïve T cell quiescence

The concept that naïve T cell quiescence might be enforced rather than the default has been debated for more than 10 years, during which time several candidate pathways have been

proposed. A good example is the transcription factor KLF2. T cells deficient in KLF2 complete thymic development, but are extremely rare in the peripheral pool and “spontaneously” upregulate activation markers, suggesting a loss of quiescence [17, 18]. Furthermore, overexpression of KLF2 causes T cells to withdraw from cell cycle (involving pathways that include inhibition of c-Myc transcription and induction of p21^{Cip1} [19–21]. Hence, this factor was proposed as a prototypical T cell quiescence factor [22].

Additional studies have caused revision of this conclusion however. KLF2 is critical for expression of molecules involved in thymic egress, in large part explaining the defect in peripheral T cells observed in *Klf2*^{-/-} animals [17, 23]. At the same time, the upregulation of T cell activation markers on KLF2-deficient T cells has been shown to arise from a non-autonomous effect, related to altered NKT cell generation in the thymus [23, 24]. Furthermore, current evidence questions a physiological role for KLF2 in cell cycle control of T cells [25]. In a mouse model in which both KLF2 and the closely related factor KLF4 are reduced in expression suggested gradual changes in T cell quiescence with aging [26], hence redundancy within this transcription factor family may complicate interpretation. Thus the precise role of the KLF family in controlling T cell quiescence remains unclear.

Recent studies indicate that a different group of transcription factors, the Forkhead box family, play a direct role in controlling naïve T cell survival and quiescence. One member of this family, Foxo1 was found to be critical for expression of IL-7R α in peripheral T cells [27–29]. As discussed, IL-7 responsiveness is crucial for naïve T cell maintenance and hence Foxo1-deficient mouse T cells decline quite rapidly (unless rescued by transgenically expressed IL-7R α [30]). These and studies with Foxo3-deficient mice [28, 30] support the idea that both Foxo1 and Foxo3 play an important role in control of naïve T cell maintenance – but these reports did not reveal a direct role for the Foxo factors in control of naïve T cell quiescence. On the other hand, evidence is mounting that a different Fox factor, Foxp1, is involved in quiescence regulation. Deletion of Foxp1 in mature T cells resulted in IL-7R α expression levels increasing (albeit modestly), and a substantial change in the naïve CD8 T cell response to IL-7: while normal mouse naïve T cells exposed to IL-7 in vitro survive but do not divide, acute deletion of Foxp1 led to IL-7-driven proliferation and differentiation toward a memory-like phenotype [31, 32]. The increase in IL-7R α expression on *Foxp1*^{-/-} T cells, while subtle, was found to contribute strongly to this effect. Intriguingly, Foxo1 and Foxp1 seem to play opposing roles in this process, resulting from Foxp1’s capacity to bind the *Il7ra* enhancer element normally occupied by Foxo1 [32]. However, Foxp1 deletion induced additional effects (including enhanced activation of the ERK pathway) that are also likely to provoke the loss of naïve T cell quiescence [32]. Hence, Foxp1 appears to operate by more than one pathway to mediate naïve T cell restraint.

Although the mechanisms by which Foxp1 (in balance with Foxo factors) regulate T cell responses are still being determined, these findings strongly support the concept that naïve T cell quiescence is tightly regulated, cells being tempered in their expression of IL-7R α (and possibly TCR signaling potential) to keep signals just below the threshold for induction of proliferation and differentiation [33].

Still, other factors have also recently been implicated in maintaining T cell quiescence. A loss-of-function mutation of Schlafen-2 (designated *Slfn2*^{eka}) causes a marked peripheral T cell deficiency, characterized by T cell apoptosis following stimulation by foreign peptide/MHC ligands or by homeostatic cues [34]. In addition, residual *Slfn2*^{eka/eka} CD8 T cells exhibit signs of partial activation -- such as CD44 upregulation but low expression of CD122 and CD127. Although this unusual phenotype was exacerbated by the T cell lymphopenia in *Slfn2*^{eka/eka} mice, further analysis showed that the CD44^{hi} CD122^{lo} population was generated even after T cell susceptibility to apoptosis was corrected (by

overexpression of Bcl-2) [34]. It is not clear, however, whether Schlafen-2 truly acts to enforce naïve T cell quiescence, rather than being required for normal differentiation of memory-phenotype cells. Nor is the function of Schlafen-2 defined at a molecular level. In any case, this factor clearly influences T cell survival and reactivity and further exploration of its function is warranted.

Interestingly, decreased naïve T cell survival and appearance of a CD44^{hi} CD122^{lo} CD8 T cell population was also observed following deletion of the tuberous sclerosis complex 1 (*Tsc1*) gene [35, 36]. Tsc1, together with its partner Tsc2, restrains the activation of mTOR, a critical regulator of metabolism that is typically induced following PI3K signaling. As in Schlafen-2 mutant animals, Tsc1 deficiency leads to substantial reduction in peripheral T cell numbers, which correlates with increased apoptotic susceptibility (and can be rescued by forced Bcl-2 expression) [35, 36]. In addition, analysis of residual naïve T cells and use of inducible knockout approaches revealed that Tsc1 loss lead to upregulation of positive regulators of cell cycle progression and various metabolic pathways [35], suggesting Tsc1 does indeed serve as a “brake” to preserve the quiescent state of naïve T cells. Additional studies indicated that the effects of Tsc1 deletion are mediated through enhanced activity of mTOR (specifically the mTORC1 complex) [35, 36], suggesting that this pathway is actively restrained in normal naïve T cells.

Whether and how Tsc-1 and Schlafen-2 might intersect to produce these related phenotypes is unclear, but will no doubt be a fruitful topic of further studies.

Beyond maintenance: Homeostatic cues that alter naïve T cell quiescence

Aside from intrinsic factors which mediate T cell quiescence, it has long been known that homeostatic cues can lead to loss of naïve T cell quiescence (in the absence of any conventional foreign antigen stimulation history. Several years ago it was found that some naïve T cells could, under certain conditions, proliferate in response to “homeostatic factors” (self peptide/MHC and IL-7). This was initially seen in situations of lymphopenia, in which competition for such ligands is reduced [6, 37]. However, studies in which IL-7 is overexpressed or administered in a non-lymphopenic setting suggest that lymphopenia is not a prerequisite for the induced expansion of naïve T cells [6, 37]. While IL-7 plays a major role in supporting such “homeostatic proliferation”, high concentrations of other “common γ -chain cytokines” such as IL-15 and IL-2 can also provoke proliferation by naïve T cells [6]. Homeostatic proliferation is thought to be important as a means of “filling” a depleted T cell niche in situations of partial immunodeficiency as, for example, occurs after certain viral infections [6, 37].

Perhaps the most remarkable feature of homeostatic proliferation is that it also induces differentiation of T cells from a naïve state to a memory-like phenotype. These so-called homeostatic memory cells arise not only in situations of artificially induced lymphopenia (as accompanies chemo- or radio-therapeutic treatments), but are also generated during “natural” lymphopenic episodes, such as the neonatal period in mice [6, 9]. In all of these situations, the “filling” of the T cell compartment is thought to limit access to available cytokine and self peptide/MHC ligands, leading to a halt in induction of any further homeostatic proliferation. However, the quiescent state of the homeostatic memory cells seems to be permanently changed, in that these cells are (like conventional memory cells) characterized by basal proliferation (driven by IL-15, at least for CD8 T cells) that differentiates the cells from their naïve precursors. Such homeostatic memory cells also acquire functional traits of conventional memory cells resulting, for example, in efficient control of bacterial infection [38]. Cells with the phenotype and function of homeostatic memory cells are found among T cells of many different foreign antigen specificities in

unimmunized and germ free mice [1, 39, 40] suggesting that this population has the diversity to participate in responses to newly encountered antigens.

A distinct pathway of altered naïve CD8 T cell quiescence has recently been identified. While generation of homeostatic memory cells was characterized as a process initiating in peripheral lymphoid tissues, studies in various gene targeted mice showed the appearance of memory-like CD8 T cells in the thymus [23, 24, 41]. Elucidation of this effect showed a surprising link between IL-4, produced by NKT (or NKT like) cells in the thymus, and generation of thymic “bystander” memory CD8 T cells [24]. IL-4, acting on the CD8 thymocytes themselves, mediates a unique effect, in that it directs upregulation of the transcription factor Eomesodermin (but not the closely related factor T-bet), which is responsible for at least some of the memory-like phenotypic changes observed [24]. While initially detected in mice with gene disruptions, such cells are also prominent in some normal mouse strains (such as Balb/c mice) [24, 42] and a similar population appears to be generated in gestational humans [43]. IL-4-dependent memory-like cells are also detected in peripheral tissues [24, 42] suggesting these cells have the opportunity to participate in “primary” immune responses.

Both of these “unconventional” memory-like CD8 T cell populations arise due to loss of quiescence of the naïve T cell pool – leading to differentiation and/or proliferation – triggered by homeostatic cues.

Naïve T cell heterogeneity in escape from quiescence

During studies on lymphopenia-driven proliferation, it became clear that not all naïve T cells are equipped to respond to these elevated homeostatic cues. In particular, reports showed that different TCR transgenic T cells varied dramatically in their ability to proliferate and differentiate in response to lymphopenia, with some clones remaining as quiescent naïve cells despite available homeostatic “space” [6, 37]. Given that TCR specificity dictates the capacity of T cells to respond to lymphopenia, it is reasonable to interpret these results to indicate a range in the presence or amount of suitable self peptide/MHC ligands in the periphery. On the other hand, this potential for homeostatic proliferation may be programmed during thymic selection (which is also, of course, dictated by the TCR) before mature T cells are tested in the periphery.

What distinguishes naïve cells that can and cannot efficiently escape quiescence in response to homeostatic cues? In mouse CD8 T cells, an intriguing correlation has been established with expression of the molecule CD5.

CD5 is best known as a negative regulator of TCR signaling, as exemplified by the capacity of CD5 knockout or overexpression studies to enhance or impair (respectively) T cell responses [44–46]. Ironically, it is mature T cells with the highest levels of CD5 that exhibit optimal capacity to undergo homeostatic proliferation in response to lymphopenia, and seem best equipped for long term survival [47–50]. This is not simply a TCR transgenic effect, as parallel findings are observed using polyclonal CD5^{hi} and CD5^{lo} cells [47–50].

The functional relevance of CD5 itself in this response is not clear however. Studies using TCR transgenic cells indicate CD5^{hi} cells also express mildly increased levels of IL-7Rα [50], which, as we have already discussed may enhance a CD8 T cell’s ability to proliferate in response to IL-7. IL-7R signaling is qualitatively similar in CD5^{low} and CD5^{high} naïve CD8 T cells, but CD5^{hi}/IL-7R^{hi} cells exhibit greater sensitivity to reduced doses of IL-7 [50]. An alternative model has been proposed based on a report that CD5^{hi} cells have an elevated density of lipid rafts (marked by the ganglioside GM1) [49]. It was suggested that increased recruitment of the IL-2 and IL-15 receptor component IL-2Rβ to these rafts could

explain the dramatic ability of CD5hi (but not CD5lo) naïve CD8 T cells to proliferate upon stimulation with IL-2 [49].

The ramifications of these findings are important [51]. Heterogeneity among the naïve T cell pool (dictated, at some stage, by the TCR interaction with self peptide/MHC) leads to a substantial range in the ability of these cells to proliferate and differentiate in response to homeostatic cues, including the cytokines IL-2, IL-7 and IL-15. Presumably, some naïve cells with the greatest potential for such responses become part of the endogenous memory pool (sometimes called “virtual memory” cells [1, 41]) present in normal mice, and hence these clones are typically not even considered when we characterize the “naïve” T cell repertoire. In addition, we might consider CD5hi naïve CD8 T cells to occupy a grey zone between naïve and memory cells: these cells are constantly poised to lose quiescence, given a change in homeostatic cues [51] (Figure 1).

Quiescence in Memory T Cells

The memory T cell pool has quite distinct requirements for long term maintenance and preservation of function, compared to the naïve T cell pool, and memory cells are considered to be sustained in a more active (i.e. less quiescent) state. The situation is made more complicated by realization that distinct memory T cell subsets display different homeostatic requirements (Box 2). In this section, we discuss the factors that regulate maintenance and oppose quiescence in the memory T cell population.

BOX 2

Quiescence among Memory T cell subsets

Memory CD8⁺ T cells, defined as expressing high levels of CD44, are extremely heterogeneous in terms of their cellular phenotype and function, and are likely to be equally diverse in their ability to survive in a quiescent state, proliferate in response to antigen, and to undergo slow basal turnover as memory cells [74]. Certain subsets of memory cells have recently been identified as poorly proliferative after microbial or viral challenge. These cells express low levels of CD62L and IL-7R α and high levels of killer cell lectin-receptor G1 (KLRG1) [75]. KLRG1⁺ cells are defined as being “terminally-differentiated” and appear to be senescent both in vitro and in vivo [76]. KLRG1⁺ cells fail to induce the transcriptional repressor Bmi-1, a molecule that is most highly expressed in hematopoietic stem cells but is also maintained in mature T cells [77]. Likewise, TCR ligation causes increased expression of Bmi-1 in KLRG1[−] cells, and results in optimal proliferation of memory cells [78]. KLRG1⁺ effector memory cells may provide useful functional contributions to the clearance of infection. However, in situations where rapidly disseminating pathogens require large numbers of responding T cells to be controlled, KLRG1[−] cells may be the optimal focus of vaccination efforts [79].

Memory T Cell Persistence and basal proliferation

Unlike naïve T cells, memory cells do not require contact with MHC class I molecules (or antigen) for their persistence [6]. Maintenance of memory CD8⁺ T cell numbers is, however, dependent on exposure to the cytokines IL-7 and IL-15, which sustain their survival and basal proliferation [52, 53]. Similar to naïve T cells, basal concentrations of IL-7 and IL-15 support survival of memory cells by up-regulating expression of molecules like Bcl-2 [54]. However, normal levels of IL-15 additionally promote the homeostatic proliferation of CD8⁺ memory T cells. This regulation is revealed by the steady decline in the antigen-primed memory population of *Il15*^{−/−} and *Il15 α* ^{−/−} [11, 55–58]. Furthermore,

when mice are treated with common γ -chain cytokine complexes (containing cytokine complexed to specific antibody, as a mechanism of delivering a strong and sustained signal through cytokine receptors), the memory CD8 T cell population undergoes rapid and extensive proliferation [59–63]. Antigen-specific memory populations are remarkably stable throughout life, which may in part be regulated by competition for these cytokines. On the other hand, the memory pool has the capacity to grow in size in response to repeated antigen encounter, suggesting secondary or tertiary memory populations may utilize distinct maintenance mechanisms [64].

Maintaining Readiness

Immunological memory is dependent on sustaining a population of cells that can respond rapidly and robustly upon a subsequent encounter with antigen. While IL-15 is important for basal proliferation and avoiding memory cell attrition, memory T cells deprived of IL-15 can still function, rapidly producing cytokines and proliferating following activation [13, 57, 58]. How are memory CD8 T cells maintained in this state of readiness?

Analysis of cell cycle stages indicate that, while most (though perhaps not all) naïve CD8 T cells are in G₀, the majority of memory T cells are in G₁, a state in which higher RNA levels allow for immediate protein synthesis, rapid functional response [65–67], and more rapid progression to cell cycle [66] (although the universality of this latter point remains controversial) [68, 69].

Intriguingly, maintaining the G₁ state in memory CD8 T cells appears to be an active process, involving contact with dendritic cells that involve engagement of CD27 and 4-1BBL, members of the tumor necrosis factor receptor superfamily, on the T cell [67]. In vitro, the blockade of such interactions leads memory cells to revert to G₀ and lose their functional potential, more closely resembling naïve T cells (at least in terms of function – phenotypic reversion of memory to “naïve-like” cells has not been clearly demonstrated) [67]. Keeping memory cells in G₁ by engagement of CD27 involves activation of the PI3K pathway [67] and leads to induction of mTOR, thus offering a potential explanation for the enhanced metabolic activity of memory cells [70]. Similarly, ligation of CD27 enhances proliferation of CD27+ human T cells, and was found to increase production of cyclin proteins that promote cell cycle progression [71]. The role of CD27 in generating functional CD8 memory cells has been long known [72, 73], but the molecular basis for these effects is still being determined.

It is intriguing to consider that, while quiescence may be actively enforced in naïve CD8 T cells, memory cells may face the opposite pressure, requiring an active signal (through CD27 and/or 4-1BB) to avoid reversion to a quiescent state.

Concluding Remarks

Both naïve and memory T cells are subject to extensive regulation in order to maintain their survival, appropriate numbers, and readiness to respond to antigen encounter. Quiescence in naïve T cells is likely to be required to reduce the energy and space required to maintain a large and diverse repertoire of lymphocytes. Survival, basal turnover and rapid functional differentiation is equally crucial for the memory CD8+ T cell compartment. In both cases, the degree of cell quiescence appears to be tightly enforced, suggesting active maintenance of naïve and memory population characteristics. Interestingly, data reviewed here suggest the line between the quiescent naïve T cell and more active memory T cell can blur as homeostatic cues fluctuate. Hence it may be time to appreciate that there are varied quiescent states among both naïve and memory pools – it will be exciting to see how these differences can be harnessed to maximize useful immune responses while avoiding

immunopathology. However, important questions remain. Much of the work that has been discussed here regards mouse CD8 T cells: Will similar principles emerge for CD4 T cells? Initial studies on, for example, the significance of CD5 expression levels [49] and the role of Foxp1 as a quiescence factor [32] suggest distinct traits for CD4 and CD8 T cells. Even less is known about the homeostatic controls that regulate human T cell quiescence: additional studies are needed to determine whether the regulatory pathways discussed here are universal mechanisms for control of T cell quiescence.

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Figure 1. Models of naïve and memory T cell quiescence

The schematic in (a) represents the conventional model, in which naïve T cells are uniformly quiescent cells, responding to homeostatic cues (including IL-7 and self peptide/MHC) as simple survival signals. Transition to the memory population occurs only through foreign antigen encounter and differentiation through an effector phase (not shown). Memory cells are less quiescent, being maintained in the G_1 stage of cell cycle and undergoing basal proliferation in response to IL-15.

Panel (b) shows a more current model, illustrating the heterogeneity in both naïve and memory pools and the capacity of T cells to move between the quiescent and active states based only on homeostatic signals. The colors of the naïve T cells correlate with CD5 expression levels on mouse naïve CD8 T cells – with CD5^{low} cells represented as blue cells, while purple cells indicate the CD5^{high} pool (which are poised to proliferate and differentiate in response to homeostatic cues). The transcription factor Foxp1 is involved in enforcing quiescence in the naïve CD8 T cell population. In the memory population, regular

encounters with Dendritic cells is important for sustaining their maintenance of G₁ phase and functional efficacy.