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Homeostatic proliferation and survival of naïve and memory T cells

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The immune system relies on homeostatic mechanisms in order to adapt to the changing requirements encountered during steady-state existence and activation by antigen. For T cells, this involves maintenance of a diverse repertoire of naïve cells, rapid elimination of effector cells after pathogen clearance, and long-term survival of memory cells. The reduction of T-cell counts by either cytotoxic drugs, irradiation, or certain viruses is known to lead to lymphopenia-induced proliferation and restoration of normal T-cell levels. Such expansion is governed by the interaction of TCR with self-peptide/MHC (p/MHC) molecules plus contact with cytokines, especially IL-7. These same ligands, *i.e.* p/MHC molecules and IL-7, maintain naïve T lymphocytes as resting cells under steady-state T-cell-sufficient conditions. Unlike naïve cells, typical "central" memory T cells rely on a combination of IL-7 and IL-15 for their survival in interphase and for occasional cell division without requiring signals from p/MHC molecules. Other memory T-cell subsets are less quiescent and include naturally occurring activated memory-phenotype cells, memory cells generated during chronic viral infections, and effector memory cells. These subsets of activated memory cells differ from central memory T cells in their requirements for homeostatic proliferation and survival. Thus, the factors controlling T-cell homeostasis can be seen to vary considerably from one subset to another as described in detail in this review.

Key words: Cytokine · Homeostasis · Lymphopenia-induced proliferation · Memory T cell · Naïve T cell

Introduction

The majority of T cells carry αβ TCR and undergo a series of selection and maturation processes in the thymus. During positive selection, T cells are tested for their ability to receive survival signals *via* TCR contact with self-peptide/MHC (p/MHC) molecules on cortical epithelial cells; cells with low but significant reactivity for self-p/MHC ligands survive (positive selection). By contrast, cells with a dangerously high affinity for self-p/MHC molecules are subjected to deletion (negative selection) *in situ* through contact with bone marrow-derived APC such as DC [1]. Most thymocytes receive no TCR signals and die locally in the thymus by "neglect". In addition to TCR stimulation, thymocytes also receive signals from contact with cytokines, especially IL-7 derived from thymic epithelial cells at the cortico-medullary junction [2]. Significantly, once mature thymocytes leave the thymus and join the peripheral pool of mature T cells, they continue to receive survival signals from IL-7 and also from self-p/MHC ligands, MHC class I molecules for $CD8^+$ cells and MHC class II molecules for $CD4^+$ cells. Thus, through constant TCR interaction with self-p/MHC ligands, positive selection continues in the extra-thymic environment and plays a vital role in maintaining T-cell viability.

Despite continuous TCR engagement with self-p/MHC molecules, post-thymic mature T cells remain immunologically naïve and stay in interphase for prolonged periods. However, when naïve

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T cells encounter foreign antigen presented by professional APC, TCR signals change from being sub-mitogenic to overtly stimulatory and lead to vigorous activation and proliferation. In addition to TCR triggering, optimal T-cell activation requires co-stimulation *via* CD28 contact with CD80/CD86 (B7.1/B7.2) on APC, and cytokine receptor signals from contact with auto-/paracrine IL-2 as well as APC-derived cytokines such as IL-12, interferon-α, and IL-15 [3–6]; these various stimuli are crucial not only for production of optimal effector functions but also for generation of functional memory cells. Conversely, T regulatory cells have been suggested to negatively regulate effector T cells, thus reducing proliferation and promoting apoptosis of these cells.

Once the pathogen is contained or eliminated, most antigen-specific T cells die, probably *via* "neglect" because of loss of contact with life-sustaining common γ chain (γ_c) cytokines and/or TCR signals [7, 8]. Loss of the majority of these now superfluous effector cells by homeostatic mechanisms thus restores the initial resting state of the immune system. However, a minor fraction of antigen-specific T cells, about 5% of the peak frequency, survives to become long-lived memory cells [7].

Memory T cells form a heterogeneous group of long-lived cells that are characterized phenotypically by high expression levels of CD45RO in humans and CD44 in mice [7, 9]. Both in humans and mice, most typical memory cells are resting cells and comprise a mixture of "central" and "effector" cells. Central memory cells retain the lymph node (LN)-homing receptors CCR7 and CD62L (L-selectin) of naïve T cells and, like the latter, recirculate through spleen and LN, whereas effector memory cells downregulate CD62L and express a diverse set of homing receptors, which enables the cells to pass through non-lymphoid tissues [9]; some effector memory cells are in an activated state and are common in chronic viral infections. Cells with a memory phenotype accumulate with age and are presumed to represent the progeny of naïve cells responding to various foreign antigens and perhaps also self-antigens. These naturally occurring cells are referred to as memory-phenotype (MP) cells. At a population level, these different T-cell subsets are kept at fairly constant numbers *via* so-called homeostatic mechanisms. Thus, homeostatic processes are crucially involved in T-cell development, survival, and maintenance, as well as following antigen-driven responses. Below, we

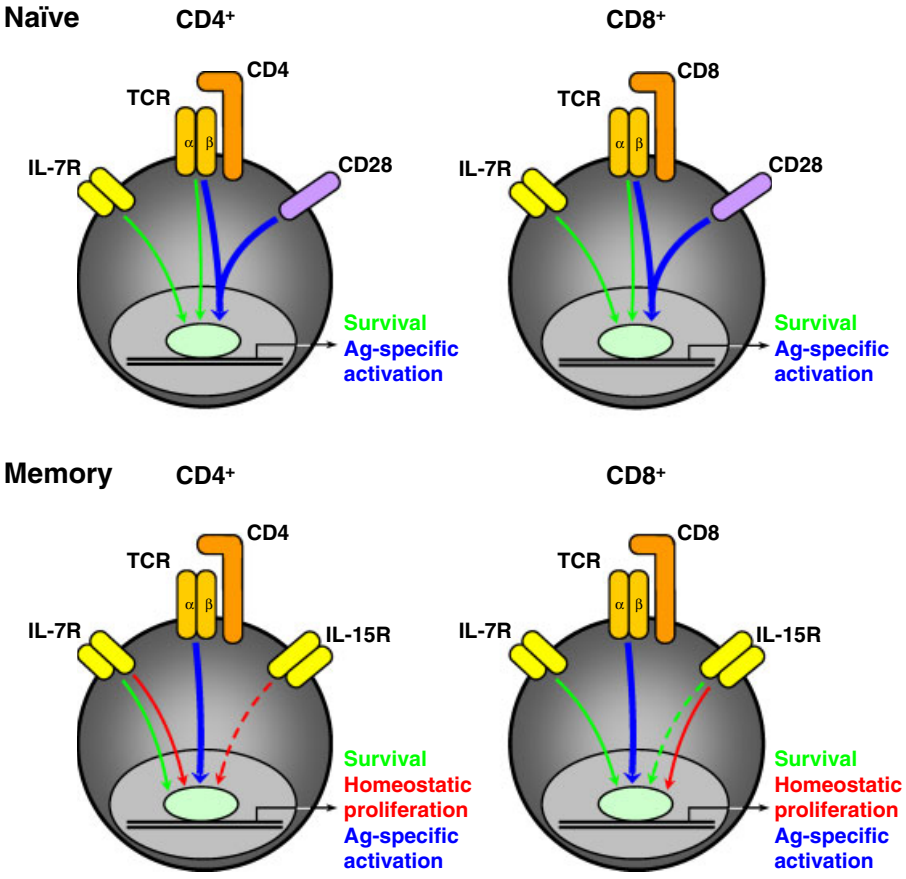

Figure 1. Survival, homeostatic proliferation, and antigen-specific activation of T-cell subsets depend on different signals. For naïve $CD4^+$ and $CD8^+$ T cells, antigen (Ag)-specific activation (in blue) of these cells requires strong TCR triggering and co-stimulatory molecules such as CD28. Conversely, survival (in bright green) of naïve T cells relies on weak stimulation of TCR and IL-7 receptor (IL-7R). Ag-specific secondary stimulation (in blue) of memory $CD4^+$ and $CD8^+$ T cells depends on a strong TCR stimulus without engagement of CD28. Survival (in bright green) of memory $CD4^+$ and $CD8^+$ T cells is TCR-independent but requires IL-7 signals, while IL-15 might also contribute to memory $CD8^+$ T-cell survival. Conversely, homeostatic proliferation (in red) of memory $CD8^+$ T cells depends mainly on IL-15, whereas memory $CD4^+$ T cells undergo homeostatic proliferation in response to both IL-7 and IL-15 signals.

will discuss homeostasis of naïve and memory cells, integrating recent advances in this field.

Naïve T cells

As mentioned in the *Introduction*, post-thymic naïve T cells depend on contact with IL-7 and self-p/MHC molecules for their homeostatic survival [8] (Fig. 1). Interaction with these stimuli generates sub-mitogenic signals that keep the cells alive and in interphase [7, 10]. Thus, naïve T cells hardly if ever divide and their numbers remain relatively stable after the onset of thymic atrophy at puberty [10]. Interestingly, contact of naïve T cells with self-p/MHC molecules does not seem to be random. Thus, for naïve $CD4^+$ T cells a recent study suggested that cells with a given specificity competed for limited self-p/MHC ligands for homeostatic survival [11]. This mechanism might contribute to the maintenance of a diverse repertoire of naïve T cells.

Recent evidence also suggested that naïve T cells have to home to secondary lymphoid organs in order to maintain a stable population size. Notably, homing of naïve T cells to the T-cell zones of secondary lymphoid organs was found to depend on their high expression levels of CCR7 and CD62L. Hence, interfering with these LN-homing molecules by blocking CD62L or genetic deletion of CCR7 ligands led to a marked decrease in total naïve T cell counts, both for $CD4^+$ and $CD8^+$ cells [12]. Interestingly, expression levels of CD62L and CCR7 on naïve $CD4^+$ and $CD8^+$ T cells have been reported to depend on transcription factors, including Kruppel-like transcription factor KLF2 and FoxO1 [13, 14]. Thus, naïve T cells in mice deficient in KLF2 or FoxO1 had a shortened life span and failed to home to secondary lymphoid organs. The requirement for migration through secondary lymphoid organs may reflect that these tissues provide an important source of IL-7. In connection with this, a subset of glycoprotein $gp38^+$ stromal cells in secondary lymphoid organs, termed fibroblastic reticular cells, has been reported to be a major source of IL-7 and also the site of secretion of the CCR7 ligand, CCL19 [12]; these cells thereby serve to both attract naïve T cells and provide them with access to extracellular matrix-associated IL-7 [15]. Significantly, fibroblastic reticular cells were found to be the only LN cell type able to convey IL-7- and CCL19-mediated survival signals to naïve T cells when co-cultured with these cells *in vitro* [12].

Apart from its role in homing, FoxO1 also seems to be involved in the regulation of CD127 (also called IL-7Rα) expression by binding to an *IL7 receptor* enhancer element [13]. Thus, FoxO1-deficient naïve T cells showed very low levels of CD127, which along with γ_c is crucial for IL-7 signaling. Hence, reduced expression of CD127 may contribute to the paucity of naïve T cells in FoxO1-deficient mice [13]. Interestingly, CD127 together with the thymic stromal lymphopoietin (TSLP)-specific receptor chain also forms the cytokine receptor for thymic stromal lymphopoietin, which is reported to contribute to homeostatic survival of total $CD8^+$ T cells [16]. In addition to FoxO1, the transcription factors PU.1, GA binding protein α (GABPα) and Growth Factor Independence-1 (GF1) have also been implicated in the regulation of CD127 expression [17–19].

Based on the above findings, homeostasis of the pool of normal naïve T cells is strictly regulated by competition for life-sustaining stimuli, notably IL-7 and appropriate self-p/MHC ligands. These stimuli are expressed in limited amounts and, at least for IL-7, require T-cell contact with specialized cells in defined regions of the lymphoid tissues. This scenario applies when the naïve pool is of normal size. As discussed below, the situation is quite different when total T-cell numbers are reduced.

When T-cell counts decrease acutely following the use of cytotoxic drugs, irradiation or infection with certain viruses, consumption of IL-7 drops, thus leading to elevated levels of IL-7. Under these conditions, self-p/MHC ligands become mitogenic for T cells and result in slow lymphopenia-induced proliferation (LIP, also termed homeostatic expansion) with gradual restoration of (near-) normal T-cell levels, a process that takes several weeks in mice [15]. Naïve T cells undergoing LIP acquire the phenotypic and functional features of memory T cells, such as high CD44 expression levels, and most of the cells eventually form resting cells resembling central memory cells generated in response to foreign antigens [15, 20]. The extent and tempo of LIP is determined by qualitative aspects of the interaction between TCR and self-p/MHC molecules. Thus, it is thought that T cells with high-affinity TCR for self-p/MHC molecules undergo faster LIP than cells with low-affinity TCR. Also, LIP of naïve cells is generally more prominent for $CD8^+$ cells than $CD4^+$ cells [15]. This disparity is not due to a difference in CD127 expression or its downstream signaling but may be partly the result of IL-7-mediated downregulation of MHC class II molecules on $CD127^+$ DC, thus selectively reducing proliferation of $CD4^+$ cells [21]. This mechanism might be crucial for the prevention of uncontrolled expansion of potentially autoreactive $CD4^+$ T cells during lymphopenia.

In addition to the TCR interaction with self-p/MHC ligands, other cell surface receptors may regulate LIP, notably co-stimulatory and co-inhibitory molecules. Thus, the co-inhibitory molecule B and T lymphocyte attenuator (BTLA, also called CD272) has been reported to dampen LIP when expressed on T cells. Accordingly, BTLA-deficient naïve $CD4^+$ and $CD8^+$ T cells were found to expand much more efficiently during LIP than their wild-type counterparts [22]. Unlike BTLA, expression of the co-stimulatory molecule CD24 (also called heat-stable antigen) on T cells has been reported to be required for optimal LIP. Thus, CD24-deficient $CD4^+$ and $CD8^+$ T cells underwent reduced LIP upon transfer to sublethally irradiated wild-type hosts [23]. Strikingly, adoptive transfer of wild-type T cells to sublethally irradiated CD24-deficient hosts led to massive LIP of donor T cells, which was due to an increased stimulatory activity of DC [23].

In contrast to mice rendered acutely lymphopenic as above, animals that are chronically lymphopenic by a complete T-cell defect, such as $TCR^{-/-}$, $RAG^{-/-}$, nude mice, or animals with severe combined immunodeficiency, lead, upon adoptive transfer

of polyclonal (but not TCR-transgenic) T cells, to a form of very rapid LIP of a fraction of donor cells, which is presumably driven by foreign antigens from commensal microflora (reviewed in [15]).

In addition to LIP, naïve T cells can be induced to proliferate in non-lymphopenic animals by increasing the intensity of IL-7 signals *via* the use of IL-7/anti-IL-7 mAb complexes. These IL-7/mAb complexes induce slow proliferation of naïve T cells, especially $CD8^+$ cells, and also MP cells (see next section) [24]. Interestingly, the tempo of slow "homeostatic" T-cell proliferation stimulated by IL-7 does not apply to other γ_c cytokines, notably IL-2 and IL-15, with these cytokines leading to a much faster form of proliferation. Thus, adoptive transfer of naïve T cells to CD122 (also called IL-2Rβ)-deficient hosts, which contain elevated levels of IL-2 and probably also IL-15, led to rapid proliferation and differentiation of donor T cells into effector cells followed by production of memory cells, thus closely resembling antigen-driven T-cell responses [25].

Central memory T cells

As mentioned earlier, numbers of memory T cells increase progressively with age and are presumed to reflect responses of naïve T cells to diverse environmental and self-antigens. Unlike naïve T cells, memory cells undergo intermittent cell division, which occurs about once every 2–3 wk for typical resting cells. Since numbers of memory cells increase only very gradually with time, cell division appears to be balanced by an equivalent degree of cell death [10]. In mice, most of the data on memory cells have come from studies on naturally occurring MP cells. The properties of these cells seem to be nearly indistinguishable from memory cells generated in response to defined antigens. In particular, both types of cells are independent of contact with self-p/MHC molecules but crucially depend on contact with a combination of IL-15 and IL-7 for homeostatic proliferation and survival [8, 15, 26–28] (Fig. 1). These properties refer to the major component of resting memory cells, which we will henceforth refer to as central memory cells. The features of the smaller subset of activated memory cells will be discussed in the next section.

Similar to naïve T cells, central memory cells recirculate between blood and the secondary lymphoid organs and enter LN *via* their high expression of CCR7 and CD62L [9]. These cells also show high surface expression of CD127 and CD122, thus allowing them to readily respond to normal levels of IL-7 and IL-15 for their survival and intermittent homeostatic proliferation [8]. As for regulation of CD127 expression by FoxO1 (see previous section), high expression of CD122 is controlled by transcription factors, namely T-bet and eomesodermin [29].

For $CD8^+$ central memory T cells, a subtle difference between MP cells and memory cells generated in response to defined antigens is that the latter rely mainly on IL-7 for their long-term survival and need IL-15 mostly for homeostatic proliferation [30–32]. By contrast, MP cells depend on a mixture of IL-7 and IL-15 for survival but again IL-15 for homeostatic proliferation [33]. This slight difference might be a consequence of how the two types of cells were initially primed. Thus, in contrast to typical antigen-induced memory cells, production of MP cells may involve rather weak TCR signals but strong signaling by γ_c cytokines such as IL-2, IL-4, IL-7, and/or IL-15. At least for MP $CD8^+$ T cells, once generated these resting central memory cells are highly sensitive to cytokines and their numbers can be considerably increased by exposure to any of the above-mentioned γ_c cytokines *in vivo*, either following injection of soluble cytokines, the use of cytokine/mAb complexes, or in cytokine-transgenic animals [8] [15] [24] [34] [35]. In addition to cytokines, chemokines are reported to affect homeostasis of central memory $CD8^+$ T cells. Thus, homeostatic proliferation of central memory $CD8^+$ T cells is impaired in mice lacking monocyte chemoattractant protein-1 (also known as CCL2) [36].

For $CD4^+$ T cells, homeostatic control of central memory and MP cells is broadly similar to $CD8^+$ T cells [8] [15] [37]. One difference is that dependency on IL-15 is less marked for $CD4^+$ cells than $CD8^+$ cells, probably because expression of CD122, a subunit of the IL-15R, is much lower on $CD4^+$ cells. As for $CD8^+$ cells, maintenance of central memory and MP $CD4^+$ cells does not require a TCR-self-p/MHC interaction. Until recently, however, the influence of MHC ligands on memory $CD4^+$ cells was controversial, largely because a high proportion of MP $CD4^+$ cells are activated cells (see next section).

Other memory T-cell subsets

The factors controlling the generation of central versus effector memory cells are still poorly understood, although the duration and strength of TCR signaling appears to be important. Thus, strong TCR signals are thought to favor the generation of effector memory T cells [9]. Unlike central memory cells, effector memory T cells are largely excluded from secondary lymphoid organs, especially LN, and accumulate in the spleen and peripheral non-lymphoid organs [9]. Similar to central memory cells, effector memory $CD8^+$ T cells undergo homeostatic proliferation, but only very slowly, perhaps reflecting the gradual death of these cells [38, 39]. Homeostatic proliferation of effector memory $CD8^+$ T cells is probably driven largely by IL-15 signaling [38]. Whether these cells also require TCR–self-p/MHC interaction is uncertain, although it is notable that effector memory cells generally show low expression of CD62L, which is a feature of cells engaged in TCR signaling.

For $CD8^+$ cells, continuous TCR signaling through contact with p/MHC ligands is needed for the maintenance of the atypical memory T cells found in mice during chronic viral infections [40–42]. These cells do not seem to be dependent on IL-15 or IL-7 as they express only low levels of CD122 and CD127 [40]. Thus, long-term survival of specific $CD8^+$ cells in chronic viral infections may be driven largely by the constant interaction of the TCR with antigen with little requirement for contact with cytokines. Cell survival in this situation can be viewed as an atypical form of

homeostatic proliferation. On this point, the memory $CD8^+$ T cells found in mice during chronic viral infections display signs of activation with low levels of CD62L, along with high expression of markers of recently activated cells such as CD43 and CD69 [40, 41]. Notably, $CD8^+$ cells found in humans infected with the human immunodeficiency virus express low levels of CD122, CD127, and CD62L [43], thus closely resembling the cells found in chronic viral infections in mice.

Interestingly, a subset of spontaneously arising $CD44^{high}$ MP $CD8^+$ T cells strongly resembles the above-mentioned memory $CD8^+$ T cells that are generated during chronic viral infections. These activated MP $CD8^+$ T cells display low CD122 surface levels and are enriched for cells expressing low levels of CD127 and CD62L, while markers indicating recent activation such as CD43 and CD69 are increased on this cell subset [44]. Notably, these $CD122^{low}$ MP $CD8^+$ T cells show a roughly threefold higher rate of homeostatic proliferation than resting $CD122^{high}$ MP cells and depend on contact with self-p/MHC class I molecules, but not γ_c cytokines, for their survival and proliferation [44]. MP $CD4^+$ T cells also contain a prominent subset of activated cells. These cells undergo rapid, p/MHC class II-dependent proliferation and are enriched in $CD122^{low}$, $CD127^{low}$, $CD62L^{low}$ cells [37]. Rapidly proliferating MP $CD4^+$ T cells are presumably responding to commensal bacteria and perhaps also to self-antigens [15].

Overall, these data suggest that memory cells engaged in chronic viral infections and their naturally occurring MP counterparts found in normal mice are maintained through continuous TCR-driven proliferation. For these cells, cytokine signals seem dispensable.

Concluding remarks and implications

For the most part, T-cell homeostasis relies on contact with a combination of self or foreign p/MHC ligands and a mixture of IL-7 and IL-15. These three factors are available in limited amounts, which restrict the size of each T-cell subset and cause the overall pool size to remain relatively constant. A recent study has challenged this view by reporting that the size of the memory $CD8^+$ T-cell compartment increased upon heterologous prime-boost immunization [45]. Thus, under these conditions a large number of effector memory $CD8^+$ T cells specific for vesicular stomatitis virus (VSV) nucleoprotein were generated, which did not impact on pre-existing MP $CD8^+$ T cells, despite similar population sizes [45]. However, the VSV nucleoprotein-specific memory $CD8^+$ T cells of this study largely comprised effector memory cells, whereas MP $CD8^+$ T cells are mainly central memory cells; these two $CD8^+$ memory T-cell subsets do not necessarily rely on the same factors for homeostasis. Furthermore, in this study the VSV nucleoprotein-specific effector memory $CD8^+$ T-cell numbers gradually declined in the blood during the memory phase [45], maybe indicating that these cells were unable to differentiate into the long-lived p/MHC class I-independent subset of cytokine-dependent central memory T cells. In connection with this point, the disparity in the types of memory T cells arising after different modes of immunization might account for why some researchers have found memory T-cell homeostasis to be p/MHC-dependent [46, 47].

The ratio of the various T-cell subsets is also influenced by other factors. Thus, the increase of MP T-cell numbers with age is due largely to gradual differentiation of naïve T cells into memory cells through constant exposure to various environmental antigens. In addition, the progressive decline of naïve T-cell numbers with age is partly a reflection of thymic involution, which is a consequence of a decrease in IL-7-producing thymic epithelial cells [2]. Also, at birth when total T-cell numbers are low, newly produced naïve T cells turn into MP cells *via* LIP [48]. Despite these alterations in the ratio of naïve to memory cells, the total size of the T-cell pool in adults remains remarkably constant throughout life.

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Abbreviations: **BTLA:** B and T lymphocyte attenuator · γ_c**:** γ chain · **LIP:** lymphopenia-induced proliferation · **MP:** memory-phenotype · **p/MHC:** peptide/MHC · **VSV:** vesicular stomatitis virus

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