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MULTI-AUTHOR REVIEW

Homeostatic maintenance of T cells and natural killer cells

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Abstract Homeostasis in the immune system encompasses the mechanisms governing maintenance of a functional and diverse pool of lymphocytes, thus guaranteeing immunity to pathogens while remaining self-tolerant. Antigen-naïve T cells rely on survival signals through contact with self-peptide-loaded major histocompatibility complex (MHC) molecules plus interleukin (IL)-7. Conversely, antigen-experienced (memory) T cells are typically MHC-independent and they survive and undergo periodic homeostatic proliferation through contact with both IL-7 and IL-15. Also, non-conventional $\gamma\delta$ T cells rely on a mix of IL-7 and IL-15 for their homeostasis, whereas natural killer cells are mainly dependent on contact with IL-15. Homeostasis of $CD4^+$ T regulatory cells is different in being chiefly regulated by contact with IL-2. Notably, increased levels of these cytokines cause expansion of responsive lymphocytes, such as found in lymphopenic hosts or following cytokine injection, whereas reduced cytokine levels cause a decline in cell numbers.

Keywords $CD4^+$ T cell · $CD8^+$ T cell · NK cell · IL-4 · IL-10 · IL-21 · Interferon · TSLP

Abbreviations

APC	Antigen-presenting cell
Blimp-1	B lymphocyte-induced maturation protein 1
BTLA	B and T lymphocyte attenuator
Foxo1	Forkhead box o1
Foxp3	Forkhead box p3
GABPα	GA binding protein α
Gfi-1	Growth factor independence 1
IFN	Interferon
IL	Interleukin
Jak	Janus kinase
KLF2	Kruppel-like factor 2
KLRG1	Killer cell lectin-like receptor G1
LCMV	Lymphocytic choriomeningitis virus
LN	Lymph node
LPS	Lipopolysaccharide
MHC	Major histocompatibility complex
MP	Memory-phenotype
NK	Natural killer
RAG	Recombinase-activating gene
$S1P_1$	Sphingosine 1 phosphate receptor 1
SOCS-1	Suppressor of cytokine signaling 1
STAT5	Signal transducer and activator of transcription 5
TCF-1	T cell factor 1
TCR	T cell receptor

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TGF-β	Transforming growth factor-β
TLR	Toll-like receptor
Treg	T regulatory cell
TSLP	Thymic stromal lymphopoietin
γ_c	Common γ chain

Introduction

Throughout their lives, lymphocytes are probed for their capacity to mount efficient responses upon contact with antigen, while maintaining self-tolerance. For $\alpha\beta$ T cell receptor (TCR)$^+$ T cells, this process starts at their precursor stage during thymic selection and continues in the periphery in antigen-naïve and antigen-experienced (memory) T cells. Extrinsic factors, most notably common γ chain (γ_c) cytokines and basal TCR signals, control and maintain a stable pool size of $\alpha\beta$ TCR$^+$ T cells from the newborn stage up to old age. Such homeostasis also applies to other lymphocyte subsets, including $\gamma\delta$ TCR$^+$ T cells and natural killer (NK) cells. Below, we will provide a brief overview on the generation and activation of typical $\alpha\beta$ TCR$^+$ T cells (hereafter referred to as T cells), followed by a systematic review of the factors governing homeostatic survival, proliferation, and expansion of T cells and other lymphocyte subsets.

T cells are scrutinized at a precursor stage in the thymus for their capacity to receive TCR-mediated survival signals (a process termed positive selection) through contact with self-peptide-loaded major histocompatibility complex (MHC) molecules on epithelial cells in the thymic cortex; these stromal cells also produce the pro-survival cytokine interleukin (IL)-7. Subsequently, negative selection deletes T cells with high affinity for self-peptide/MHC molecules on professional antigen-presenting cells (APCs) and epithelial cells in the medulla [1]. Upon completion of these steps, mature CD4$^+$ and CD8$^+$ thymocytes are released into the periphery and join the pool of naïve T cells. At this stage, naïve T cells rarely, if ever, undergo cell division but continuously screen the surface of APCs in secondary lymphoid organs for their cognate antigen. Upon encounter with antigen on activated APCs, naïve T cells become fully stimulated and undergo massive proliferation and expansion, thereby giving rise to effector T cells that are able to kill target cells and release effector cytokines [2]. The majority of effector T cells are characterized by high expression of killer cell lectin-like receptor G1 (KLRG1), and most of these cells are eliminated via apoptosis upon clearance of the pathogen concerned, leaving a few antigen-specific T cells characterized by high IL-7 receptor α (CD127) surface expression to survive as memory T cells [3]. Compared to their naïve counterparts, memory T cells have the ability to mount more rapid and enhanced immune responses upon renewed contact with the same pathogen or antigenic determinant [2].

Typical memory T cells are long-lived and migrate between the secondary lymphoid organs via lymph and blood. These so-called "central" memory T cells express specific homing molecules, namely chemokine receptor CCR7 and CD62L (L-selectin), which enable their migration to the T cell zones of lymph nodes (LNs) [4]. Conversely, expression of these homing molecules is very low on another memory T cell subset found mainly in peripheral tissues and blood, termed "effector" memory T cells [4–6]. Both subsets are characterized by high surface expression of the adhesion molecule CD44 (CD44^{high}), whereas naïve T cells have a CD44^{low} phenotype. It should be noted that small numbers of polyclonal T cells with a memory-phenotype (MP) are found in unimmunized animals; many of these MP cells are thought to arise through contact with self-antigens [7]. Unless stated otherwise, the discussion of memory and MP T cells below refers to central rather than effector memory cells.

T cells

T cell receptor signals

Once T cells have exited the thymus, they are dependent on the same pattern of survival signals they received during their development in the thymus. In particular, survival of antigen-naïve T cells requires continued contact with self-peptide/MHC molecules, MHC class II for CD4$^+$ T cells, and MHC class I for CD8$^+$ T cells [8–12]. Notably, the survival signals delivered via TCR contact with self-peptide/MHC molecules are peptide specific, and there is considerable competition among naïve T cells of a given antigen specificity for contact with appropriate self-peptide/MHC molecules [13]. Significantly, this TCR-self-peptide/MHC interaction does not induce naïve T cells to proliferate and attack self, but rather, in synergy with IL-7, provides low-level signals that maintain cell survival in interphase [14, 15]. Contact with these survival factors occurs in secondary lymphoid organs, such as LNs, where professional APCs and local stromal cells provide a rich source of MHC molecules and IL-7, respectively [15–18]. In line with this model, numbers of naïve T cells are significantly reduced under conditions where homing to LNs is hampered because of decreased levels of CD62L or CCR7. Thus, antibody-mediated blocking of CD62L or deficiency of the transcription factors Kruppel-like factor 2 (KLF2) or forkhead box o1 (Foxo1) leads to reduced levels of CD62L, CCR7, and sphingosine 1 phosphate receptor 1 ($S1P_1$), and is associated with a severe reduction in naïve T cell numbers [19–21].

In contrast to naïve T cells, memory T cell homeostasis does not require TCR contact with MHC molecules [22–25]. However, under certain circumstances, memory T cells remain dependent on peptide/MHC molecules, for example during chronic infections and autoreactive responses against self-antigens [15, 26]. The observations from acute and chronic viral infection models emphasize that memory $CD8^+$ T cells of identical pathogen specificity rely, depending on the pathophysiological context, on distinct mechanisms to assure their maintenance. Thus, memory $CD8^+$ T cells generated following acute infections depend on a mix of particular cytokines (see below) for their survival and homeostatic proliferation, whereas memory $CD8^+$ T cells forming during chronic infections require contact with cognate antigen/MHC molecules [15, 25, 26].

For $CD4^+$ T regulatory cells (Tregs), whether homeostasis of these cells requires contact with self-peptide/MHC molecules is controversial. In one study, mice expressing MHC class II molecules selectively on thymic cortical epithelial cells, but not in peripheral tissues, contained a comparably normal pool size of Tregs, suggesting that post-thymic Tregs do not require contact with self-peptide/MHC molecules [27]. Conversely, a more recent study using mice with abrogated TCR signaling capacity showed decreased homeostatic proliferation of Tregs in vivo [28].

Cytokines sharing the common γ chain receptor

The γ_c receptor (CD132) is a subunit of the cytokine receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, all of which play crucial roles during lymphocyte generation, survival, and homeostasis. For all γ_c cytokines, selectivity for individual cytokines is determined by their private α chain [29]. Moreover, for IL-2 and IL-15, a shared β subunit for the IL-2 and IL-15 receptor (CD122) is involved in cytokine binding and signaling. Cytokine binding and signaling through γ_c leads to the activation of different signal transduction molecules, including signal transducer and activator of transcription (STAT) 5A and 5B, Janus kinase (Jak) 1 and 3, and, in the case of pro-survival signals to T cells, favorably shifts the balance between anti-apoptotic (e.g., Bcl-2) and pro-apoptotic (e.g., Bim) molecules towards the former [29, 30]. Synthesis of γ_c cytokines can occur in both immune and non-immune cells. Thus, IL-2 is produced mainly by activated T cells, predominantly $CD4^+$ T cells, in secondary lymphoid organs and, to a lesser extent, also by NK cells, NK T cells, and activated dendritic cells [31]. For IL-7, stromal cells in primary and secondary lymphoid organs secrete high amounts of IL-7 at a constant rate, followed by its presentation on extracellular matrix in these lymphoid as well as non-lymphoid organs (e.g., skin, intestine, and liver) [17, 32–34] (Fig. 1). Also, hepatocytes can produce relevant amounts of IL-7, for example upon treatment of mice with lipopolysaccharide (LPS) [33]. IL-15 is synthesized in APCs upon triggering with Toll-like receptor (TLR) agonists, such as poly(I:C) and LPS, leading to autocrine stimulation of APCs via type I interferon (IFN-I) [35]. Alternatively, IL-15 can be produced following activation of APCs with type II IFN, such as IFN-γ derived either from NK cells stimulated with IL-12 and IL-18, activated

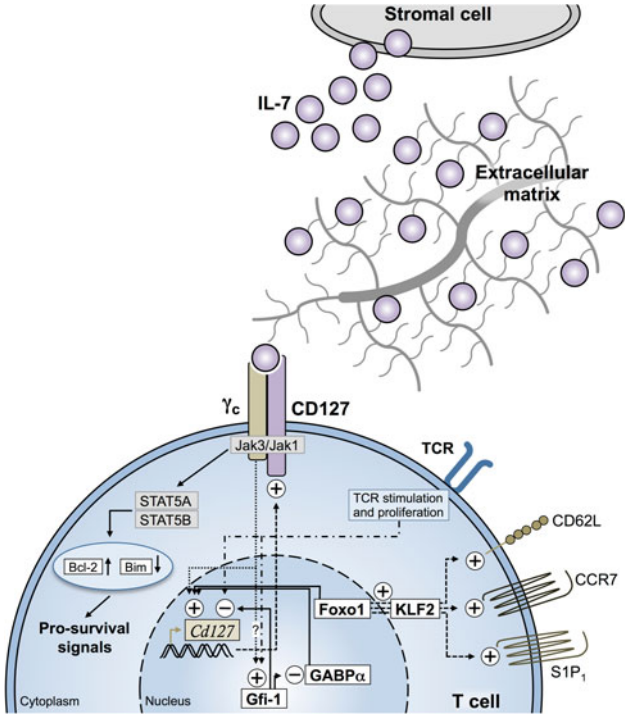

Fig. 1 Regulation of the IL-7 receptor α chain CD127. IL-7 (*light purple dots*) is usually produced at a constant rate by stromal cells residing in the primary and secondary lymphoid organs. Subsequently, IL-7 accumulates on extracellular matrix and is presented to lymphocytes, here a T cell, expressing the IL-7 receptor, composed of the γ_c (*light brown bar*) and the IL-7 receptor α chain CD127 (*purple bar*). Both these IL-7 receptor subunits contain cytoplasmic tails interacting with signaling molecules, such as Jak 1 and 3. Signals emerging from Jak 1 and 3 lead, via activation of STAT5A and 5B, to the upregulation of anti-apoptotic proteins such as Bcl-2 and downregulation of pro-apoptotic proteins such as Bim in mitochondria (*light blue oval*), thus tipping the balance in favor of pro-survival signals. Transcription of the *Cd127* gene and thus upregulation of CD127 is positively influenced by contact with γ_c cytokines, GABPα, and Foxo1. Foxo1 enhances expression of KLF2 thus leading to upregulation of the chemokine receptor CCR7, CD62L (L-selectin), and $S1P_1$. Conversely, under certain conditions, contact with pro-survival γ_c cytokines may induce activation of Gfi-1 in vitro, which either directly or via inhibition of GABPα may downregulate CD127. Moreover, strong TCR stimulation (and proliferation) may also lead to decreased CD127 expression, either directly or via activation of Gfi-1. *Foxo1* forkhead box o1, *Gfi-1* growth factor independence 1, *Jak* Janus kinase, *KLF2* Kruppel-like factor 2, *STAT5* signal transducer and activator of transcription 5, *TCR* T cell receptor, *$S1P_1$* sphingosine 1 phosphate receptor 1, *γ_c* common γ chain

NK T cells, or effector T cells [36]. Subsequently, APCs synthesize IL-15 and transport it to their surface in association with IL-15Rα, where it is presented *in trans* to IL-15-sensitive T and NK cells [37] (Fig. 2). As discussed in detail in the following sections, IL-7 and IL-15 are crucial for homeostatic survival and proliferation of

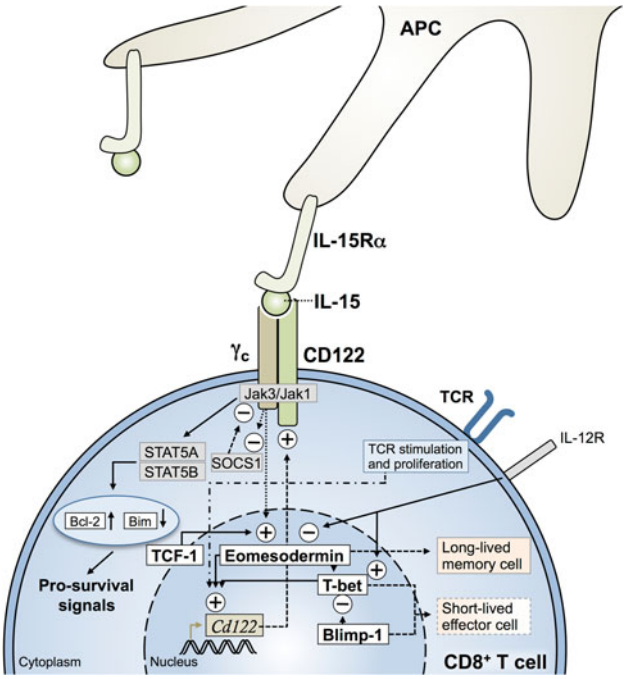

Fig. 2 Regulation of the IL-15 receptor *β* chain CD122. IL-15 (*light green dots*) is produced by APCs along with its α chain IL-15Rα. Upon intracellular association of IL-15 with IL-15Rα, both are transported onto the surface of the APC and presented *in trans* to lymphocytes, here a $CD8^+$ T cell, expressing the dimeric IL-15 receptor, composed of the γ_c (*light brown bar*) and the IL-15 receptor *β* chain CD122 (*light green bar*). (Notably, IL-15-responsive lymphocytes may also express IL-15Rα on their own surface, which is not shown here.) Both these IL-15 receptor subunits contain cytoplasmic tails interacting with signaling molecules, such as Jak 1 and 3. Signals emerging from Jak 1 and 3 lead, via activation of STAT5A and 5B, to the upregulation of anti-apoptotic proteins such as Bcl-2 and downregulation of pro-apoptotic proteins such as Bim in mitochondria (*light blue oval*), thus favoring pro-survival signals. SOCS1 is able to directly inhibit the activity of Jak 1 and 3 and thus negatively influence IL-15-mediated signaling. Transcription of the *Cd122* gene and thus upregulation of CD122 is positively influenced by the combined action of eomesodermin and T-bet, or by TCR stimulation (and proliferation). Conversely, Blimp-1 represses T-bet thereby negatively influencing *Cd122* transcription. Contact with IL-12 or signals from APCs upon CpG binding to TLR9 on APCs (not shown) leads to inhibition of eomesodermin, whereas these signals activate T-bet. In contrast, contact with γ_c cytokines and TCF-1 activity positively influence eomesodermin, which favors the generation of long-lived memory $CD8^+$ T cells, whereas Blimp-1 together with T-bet favors the generation short-lived effector $CD8^+$ T cells. *APC* antigen-presenting cell, *Blimp-1* B lymphocyte-induced maturation protein 1, *Jak* Janus kinase, *SOCS-1* suppressor of cytokine signaling 1, *STAT5* signal transducer and activator of transcription 5, *TCF-1* T cell factor 1, *TCR* T cell receptor, *TLR* Toll-like receptor, γ_c common γ chain

conventional T cells, whereas IL-2 signals are essential for the homeostasis of Tregs [38, 39].

The major role of IL-2 in vivo appears to be in mediating development and homeostasis of Tregs, thus maintaining peripheral immune tolerance [39]. $CD4^+$ Tregs typically express high levels of IL-2Rα (CD25) and the transcription factor Foxp3, the latter being essential for Treg function [40]. Optimal expression of Foxp3 and CD25 is dependent on contact with IL-2 [40]. Moreover, in conjunction with transforming growth factor (TGF)-*β*, IL-2 signals are also crucial during Treg development in the thymus, as well as for homeostatic proliferation and survival of Tregs in peripheral LNs [39–43]. Thus, IL-$2^{-/-}$, $CD25^{-/-}$, and $CD122^{-/-}$ mice, which all lack normal IL-2 signaling, show a considerable reduction in Treg numbers, thereby leading to systemic autoimmune disease in these mice [39–41]. Conversely, Treg numbers increase several-fold in lymphoid and non-lymphoid organs of mice receiving injections of IL-2 in the form of recombinant IL-2 mixed with a particular anti-IL-2 monoclonal antibody (mAb); such IL-2/anti-IL-2 mAb complexes focus IL-2 onto $CD25^+$ cells and expand these cells [44, 45]. It should be noted that, although Tregs consume IL-2 and express a high level of CD25 under steady-state conditions, these cells do not produce IL-2 [39]. Thus, it has been suggested that Tregs might exert some of their suppressive function by consumption of IL-2 (and other pro-survival γ_c cytokines) via their high surface density of CD25 [31, 46]. Notably, certain other immune cells as well as some non-immune cells express CD25, albeit at much lower levels, and blocking CD25 on these cells with antibody or the use of $CD25^{-/-}$ mice also leads to high levels of IL-2, thereby causing strong IL-2-mediated proliferation of MP $CD8^+$ T cells [31, 47, 48]. In contrast to IL-2, administration of IL-4 to normal mice led to a reduction of $CD4^+$ $Foxp3^+$ Tregs [49].

With regard to conventional T cells, several recent studies have revisited the role of IL-2 during priming of naïve T cells and shown that provision of IL-2 is important for inducing optimal T cell responses [48]. Thus, IL-2 signals during priming of naïve $CD4^+$ and $CD8^+$ T cells optimize expansion of these cells and allow them to survive as long-lived memory cells, in part due to IL-2-induced high expression of CD127 on the cells [50, 51]. Moreover, for $CD8^+$ T cells, it has been shown that contact with IL-2 during primary infection with the lymphocytic choriomeningitis virus (LCMV) allows antigen-specific memory $CD8^+$ T cells to efficiently respond to secondary challenge with the same virus [52, 53]. However, in addition to the qualitative effects of receiving IL-2 signals during priming, contact with IL-2 can have a quantitative effect on CD25 expression on effector T cells. Thus, effector T cells showing prolonged expression of high CD25 generally become short-lived effector cells, whereas the fraction of

cells that upregulate CD25 for a shorter period (thereby receiving less stimulatory signals) tend to survive as long-lived memory cells [51, 54]. At the memory stage, administration of recombinant IL-2 to mice 2 months following LCMV infection has been shown to mediate proliferation and expansion of virus-specific memory $CD8^+$ T cells and also, to a lesser degree, $CD4^+$ T cells [55, 56]. Vigorous expansion of LCMV-specific memory $CD8^+$ T cells and also naturally occurring MP $CD8^+$ T cells was observed upon adoptive transfer of these cells to normal mice treated with IL-2/anti-IL-2 mAb complexes [44, 57]. These observations are in line with studies on antigen-specific $CD8^+$ T cells from mice lacking the co-inhibitory molecule B and T lymphocyte attenuator (BTLA, CD272). Thus, $BTLA^{-/-}$ $CD8^+$ T cells showed enhanced primary and secondary antigen responses in vivo, presumably reflecting that BTLA engagement inhibits IL-2 secretion by T cells [58, 59].

Besides its essential contribution to B cell development (in mice), IL-7 in concert with tonic TCR signals has a crucial role in maintaining the survival of naïve $CD4^+$ and $CD8^+$ T cells in interphase. IL-7 also contributes to the survival and intermittent homeostatic proliferation of memory T cells [56, 60, 61] (Fig. 3). Thus, it is not surprising that virtually all T cells express high levels of IL-7Rα (CD127). Downregulation of CD127 occurs following TCR engagement in vivo or after contact with IL-2, IL-4, IL-6, IL-7, or IL-15 in vitro [62–64], although the role of these cytokines in decreasing CD127 levels in vivo is controversial [44, 65, 66]. Conversely, several transcription factors including Foxo1 and GA binding protein α (GABPα) have been implicated in the upregulation of CD127 in T cells (Fig. 1), as well as PU.1 in pre-B cells [20, 67, 68]. Moreover, the transcription factor growth factor independence (Gfi)-1 has been reported to repress CD127 in $CD8^+$ T cells by antagonizing GABPα following TCR signals in vivo or contact with IL-2, IL-4, IL-6, IL-7, or IL-15 in vitro [64, 69].

Interestingly, IL-7 signals also influence lymphoid tissue inducer cells, which are crucial for the development of secondary lymphoid organs, including LNs and Peyer's patches. Lymphoid tissue inducer cells are retinoic acid-related orphan receptor (ROR)γt^+ $CD4^+$ $CD3^-$ cells in the gut. It has been shown that these cells depend on IL-7 signals, and that increased IL-7 signals lead to the expansion of these cells in vivo [70–72].

Unlike IL-7, responsiveness to IL-15 (and IL-2) is controlled by expression of CD122, the IL-2/IL-15Rβ subunit. Expression of CD122 is regulated by many factors, including upregulation following TCR stimulation. In particular, the T-box transcription factor eomesodermin in conjunction with T-bet ensures maintenance of high CD122 levels on long-lived MP $CD8^+$ T cells [73, 74].

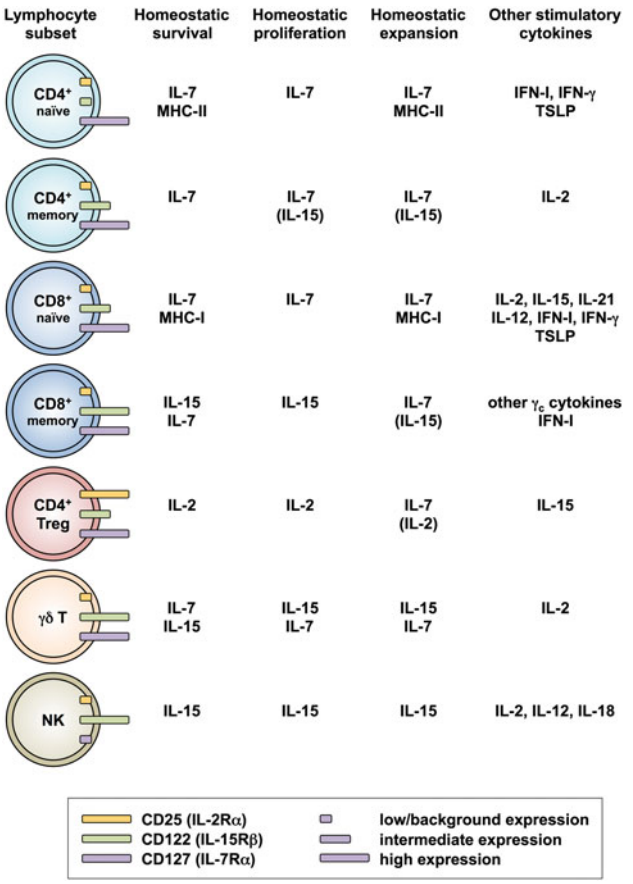

Fig. 3 Factors involved in the homeostasis of T cells and NK cells. Lymphocyte subsets are depicted in different colors (*blue* conventional $CD4^+$ and $CD8^+$ T cells; *red* Treg; *light orange* γδ T cell; *light brown* NK cell), along with their expression of CD25 (IL-2Rα *orange bar*), CD122 (IL-15Rβ *light green bar*), and CD127 (IL-7Rα *purple bar*). Expression levels of these cytokine receptors on these lymphocyte subsets are indicated by the size of the *bars* as low (or background), intermediate, or high. Homeostatic survival and expansion of naïve $CD4^+$ and $CD8^+$ T cells depends on IL-7 and MHC molecules, whereas their homeostatic proliferation requires IL-7 signals. Other cytokines able to stimulate naïve T cells, e.g., upon injection into mice, are IFN-I (i.e., IFN-α/β), IFN-γ, and TSLP, as well as, for naïve $CD8^+$ T cells, also IL-2, IL-15, IL-21, and IL-12. Homeostasis of typical memory $CD4^+$ T cells is governed by IL-7 (and IL-15) signals, whereas contact with IL-15 and IL-7 is responsible for homeostasis of typical memory $CD8^+$ T cells, which can also be boosted by administration of other γ_c cytokines and IFN-I. Tregs rely on IL-2 for homeostatic survival and proliferation, while their homeostatic expansion is dependent on IL-7 and probably also IL-2. For γδ T cells, contact with mainly IL-15 and also IL-7 is responsible for their maintenance, whereas IL-15 signals are crucial for NK cell homeostasis. *IFN-I* type I interferon, *MHC* major histocompatibility complex, *MHC-I* MHC class I, *MHC-II* MHC class II, *NK* natural killer, *Treg* T regulatory cell, *TSLP* thymic stromal lymphopoietin, γ_c common γ chain

Eomesodermin is influenced positively by the transcription factor T cell factor (TCF)-1 as well as by γ_c cytokine signals, whereas inflammatory stimuli (such as IL-12 and CpG) have been found to repress eomesodermin but induce

T-bet expression; conversely, T-bet together with B lymphocyte-induced maturation protein (Blimp)-1 favors the generation of short-lived effector $CD8^+$ T cells [51, 75–81] (Fig. 2). CD122 expression is highest on both memory and MP $CD8^+$ T cells, as well as on NK cells and certain other lymphoid subsets [35, 57, 82]. Accordingly, IL-15 signals are crucial for the homeostatic proliferation and survival of each of these subsets (Fig. 3). Contact with IL-15 occurs in several sites, including the bone marrow, spleen, and LNs, as well as liver [82–87]. The importance of IL-15 is indicated by the finding that animals deficient in IL-15 production ($IL\text{-}15^{-/-}$ mice) or IL-15Rα-mediated transpresentation of IL-15 ($IL\text{-}15R\alpha^{-/-}$ mice) show a considerable reduction in numbers of resting MP $CD8^+$ T cells, NK cells, NK T cells, and intraepithelial lymphocytes; these findings reflect that IL-15 is required largely for proliferation and expansion of these cells rather than for their initial formation [83, 88–90]. Conversely, increasing IL-15 signals in vivo, for example by injecting recombinant IL-15 or the use of IL-15 transgenic animals, causes considerable expansion of MP $CD8^+$ T cells and NK cells [91–96].

IL-21, which is mainly produced by $CD4^+$ T cells, is able to act on $CD8^+$ T cells, either by itself or in synergy with IL-15 (see below), to enhance $CD8^+$ T cell responses or counts [97–99]. Recently, IL-21 signals delivered to $CD8^+$ T cells during viral infection were found to be important for the formation of memory $CD8^+$ T cells [100]. Moreover, for memory $CD8^+$ T cells forming during chronic virus infections, IL-21 signals were able to prevent rapid exhaustion of these cells, thus helping to control the virus [101–103]. However, injection of IL-21 did not accelerate homeostatic proliferation of memory $CD4^+$ and $CD8^+$ T cells generated following acute virus infections [56].

Notably, some γ_c cytokines can act in synergy with other γ_c cytokines. Thus, in contrast to IL-15 alone, which has little effect on naïve $CD8^+$ T cells at physiological concentrations [35], a combination of exogenous IL-15 and IL-21 is able to induce proliferation not only of memory but also naïve $CD8^+$ T cells in vitro and lead to increased $CD8^+$ T cell-mediated anti-tumor activity in vivo [98]. Also, IL-15 signals can be supplemented or compensated for by high concentrations of other γ_c cytokines, such as by injecting IL-2, IL-4, or raising IL-7 levels in IL-7 transgenic mice. These situations lead to marked increases in numbers of MP $CD8^+$ T cells, even in $IL\text{-}15^{-/-}$ mice. Except in IL-7 transgenic mice, elevating the level of γ_c cytokines induces rapid proliferation, as distinct from the slow intermittent proliferation, characteristic of normal MP T cell homeostasis [44, 104]. For IL-7, high levels of thymic stromal lymphopoietin (TSLP), which does not bind to γ_c but to CD127 and the TSLP receptor, can compensate for a lack of IL-7 in T cell homeostasis in vivo [105, 106].

Increased availability of γ_c cytokines, especially IL-7 and to a lesser degree IL-15, is found during lymphopenia, which occurs naturally in the neonatal period of mice or upon removal of T and B cells from adults, for example following whole body irradiation [15, 107]. Lymphopenia reduces consumption of IL-7 (and IL-15), thereby increasing its availability to residual T cells and after adoptive T cell transfer to lymphopenic hosts [15, 108]. As a result, both conventional T cells and Tregs are subjected to increased IL-7 (and IL-15) signaling, thereby causing the cells to undergo acute "homeostatic" proliferation, also termed homeostatic expansion or lymphopenia-induced proliferation [109–112]. For naïve T cells, homeostatic expansion is dependent not only on IL-7 but also on TCR contact with self-peptide/MHC complexes. Following homeostatic expansion, naïve T cells acquire the phenotypic and functional properties of memory T cells. As mentioned earlier, most MP T cells may be self-reactive and represent the progeny of naïve T cells responding to self-antigens during episodes of homeostatic expansion [7, 109–111, 113, 114]. Interestingly, lack of suppressor of cytokine signaling (SOCS)-1 renders naïve $CD8^+$ T cells hyperresponsive to IL-15 signals, thus causing self-peptide/MHC molecule-dependent "homeostatic expansion" even under non-lymphopenic conditions [115, 116]. Moreover, under conditions where in vivo levels of either IL-2 or IL-15 are elevated, naïve T cells undergo a form of homeostatic expansion that is MHC-dependent, but much more rapid than the typical pattern of slow homeostatic expansion driven by IL-7 [117]. In addition to cytokines and self-peptide/MHC molecules, homeostatic expansion of T cells can be influenced by other factors such as expression of lymphocyte activation gene-3 (LAG-3, CD223), BTLA (CD272), the transmembrane adaptor protein SIT, and heat-stable antigen (CD24). Thus, homeostatic expansion of LAG-3-, BTLA-, or SIT-deficient naïve $CD8^+$ T cells is faster and more intense than for normal cells [59, 118, 119]. Conversely, CD24-deficient T cells show a considerable reduction in their tempo of proliferation during homeostatic expansion [120]. For homeostatic expansion of memory T cells, it should be mentioned that these cells are heavily dependent on contact with both IL-7 and IL-15, but do not require interaction with peptide/MHC molecules [15].

Other cytokines

As mentioned above, IFNs, particularly IFN-α/β (IFN-I), can lead to IL-15 production by APCs and thereby induce proliferation of memory and MP $CD8^+$ T cells. In addition, IFN-I is also able to act directly on naïve antigen-specific

$CD8^+$ and $CD4^+$ T cells and promote expansion and survival of these cells during an immune response, such as following infection with LCMV [121, 122]. This direct action of IFN-I provides a so-called "third signal" to the responding T cells and can also be delivered by IL-12 [123]. In certain situations, however, IFN-I might exert a negative role on $CD8^+$ T cells following viral infection, particularly on memory $CD8^+$ T cells [124]. With regard to other cytokines, IFN-γ has been found to resemble IFN-I in being able to act directly on naïve $CD8^+$ and $CD4^+$ T cells by improving antigen-mediated expansion of these cells [125, 126] (Fig. 3).

Certain cytokines, notably TGF-β and IL-10, are produced by some Tregs and can have a marked inhibitory action on T cells, although data from recent years have shown that the contribution of these cytokines to the quality of the immune response is highly variable, especially for $CD8^+$ T cells [127]. Thus, in certain situations, IL-10 can boost expansion and memory formation of antigen-specific $CD8^+$ T cells, for example during acute bacterial infection [128, 129]. However, during prolonged immune responses, IL-10 seems to be suppressive. Thus, in chronic LCMV infection, it was found that blocking IL-10 production, either by genetic removal or injection of antibody, reversed the anergic phenotype of antigen-specific $CD8^+$ and $CD4^+$ effector T cells, thereby leading to virus clearance and the generation of functional antigen-specific memory T cells [130, 131].

For TGF-β, this cytokine has a role in regulating the survival and differentiation of Tregs and effector $CD4^+$ T cells [39, 132]. Conversely, for $CD8^+$ T cells, TGF-β signals might influence responsiveness of $CD8^+$ T cells to homeostatic cues, such as TCR and cytokine signals [132]. Thus, T cell-targeted deletion of the TGF-β receptor II led to the emergence of activated, effector-like $CD62L^{low}$ $CD44^{high}$ $CD8^+$ T cells undergoing rapid homeostatic proliferation [132]. Based on these characteristics, TGF-β receptor-deficient $CD8^+$ T cells display features of memory T cells that continue to interact with their cognate (self-)antigen. Interestingly, a recent study showed that attenuation of TGF-β signaling in T cells resulted in a reversal of the anergic phenotype of antigen-specific memory $CD8^+$ T cells generated during a chronic viral infection, thus leading to eradication of the virus [133].

$\gamma\delta$ T cells

T cells expressing $\gamma\delta$ TCRs are non-conventional T cells that recognize non-peptide antigens, which are upregulated upon tissue stress [134, 135]. Recognition of these stress-induced molecules by $\gamma\delta$ T cells is achieved via binding of their (semi-)invariant $\gamma\delta$ TCRs in addition to triggering of other stimulatory molecules, such as TLRs. In addition to being present in secondary lymphoid organs and the liver, $\gamma\delta$ T cells reside in epithelial surfaces, such as the skin and the mucosa of the respiratory, digestive, and reproductive systems [134, 135]. Homeostasis of $\gamma\delta$ T cells has been reported to require contact with cytokines, but not with MHC molecules. Thus, γ_c cytokines, notably IL-7 and IL-15, have been implicated in mediating these processes, as mice deficient in these cytokines or their receptors lack (subsets) of $\gamma\delta$ T cells [89, 136–139]. Accordingly, $\gamma\delta$ T cells express high levels of CD127 and CD122 [140]. Similar to $\alpha\beta$ TCR^+ T cells and NK cells, injection of $\gamma\delta$ T cells to lymphopenic hosts also lacking $\gamma\delta$ T cells leads to homeostatic expansion of transferred $\gamma\delta$ T cells, which is driven by IL-15 and IL-7 [140, 141]. Thus, $\gamma\delta$ T cells compete for the same cytokine signals as T cells, notably $CD8^+$ $\alpha\beta$ TCR^+ T cells, and NK cells during homeostatic expansion, while contact with MHC molecules does not seem to be required for such expansion [141]. Interestingly, an $NK1.1^+$ subset of $\gamma\delta$ T cells shows a slower rate of homeostatic expansion, compared to $CD8^+$ $\gamma\delta$ T cells [142]

Natural killer cells

IL-2 is known as a potent NK cell stimulatory factor, both in vitro and in vivo, and NK cells expand considerably following treatment with CD122-specific IL-2/anti-IL-2 mAb complexes, similar to MP $CD8^+$ T cells [44, 57, 143]. However, IL-2 probably plays only a minor role in the steady-state homeostasis of NK cells, in contrast to IL-15, which is crucial for survival and homeostatic proliferation of NK cells under normal conditions [144] (Fig. 3). As mentioned above, IL-$15^{-/-}$ and IL-$15R\alpha^{-/-}$ mice both lack NK cells, whereas increased IL-15 signals in vivo lead to expansion of NK cells [89–95]. Conversely, the peripheral pool size of NK cells in IL-$2^{-/-}$ IL-$4^{-/-}$ IL-$7^{-/-}$ triple-deficient mice on a recombinase-activating gene $(RAG)^{-/-}$ background is normal and functional, thus showing that these γ_c cytokines are dispensable for NK cell generation and survival [145]. Interestingly, IL-15-mediated expansion of NK cells is antagonized by IL-21 in vitro, whereas NK cells receiving IL-21 signals show enhanced cytotoxicity and IFN-γ production upon stimulation with poly(I:C) in vivo or IL-15 in vitro [146].

Similar to T cells, NK cells undergo expansion upon transfer to lymphopenic mice and, like MP T cells, acquire characteristics of long-lived memory cells [147]. However, such "homeostatic expansion" requires adoptive transfer of NK cells to NK cell-deficient mice, notably $RAG^{-/-}$ $\gamma_c^{-/-}$ double knockout mice. Such $RAG^{-/-}$ $\gamma_c^{-/-}$ mice probably contain increased cytokine levels of both IL-7 and IL-15, reflecting a lack of consumption of these cytokines [144, 148]. Moreover, in very young mice, i.e., at the age of 1 month or less, turnover of NK cells is considerably

increased, suggesting that NK cells, like MP $CD8^+$ T cells, undergo homeostatic expansion [149]. Such expansion of NK cells probably depends largely on contact with IL-15, with little or no role for IL-7 or other γ_c cytokines [145]. Interestingly, $KLRG^+$ NK cells show poor IL-15 responses in terms of homeostatic proliferation and homeostatic expansion [148]. Also, MHC class I molecules do not seem to be involved in homeostatic NK cell expansion [149].

IL-12 and IL-18 are able to activate NK cells when added in vitro. However, neither of these cytokines nor IFNs have been implicated in the normal homeostasis of NK cells in vivo. Likewise, there is no evidence that NK cell homeostasis involves TGF-β or IL-10.

Concluding remarks and summary

Collectively, homeostasis of lymphocytes is governed by cytokines, most notably γ_c cytokines, and, for some lymphocytes, also signals received from antigen-receptors (Fig. 3). Thus, homeostatic survival and homeostatic expansion of naïve $CD4^+$ and $CD8^+$ T cells depends on IL-7 and self-peptide/MHC molecules, whereas homeostatic proliferation of these cells requires IL-7 (and IL-15) signals. Other cytokines able to stimulate naïve $CD4^+$ T cells are IFNs and TSLP, whereas naïve $CD8^+$ T cells can also be stimulated with increased levels of IL-2, IL-15, IL-21, and IL-12.

Homeostasis of typical (central) memory and MP $CD4^+$ T cells is governed by IL-7 (and IL-15) signals, whereas contact with IL-15 and IL-7 is responsible for homeostasis of typical (central) memory and MP $CD8^+$ T cells. Elevated levels of other γ_c cytokines, e.g., following injection of recombinant cytokine or IFN-I, are able to boost numbers of memory $CD8^+$ T cells, while enhanced IL-2 signals can lead to an increase in memory $CD4^+$ T cell counts. Notably, both MP cells and memory $CD8^+$ T cells generated by homeostatic proliferation closely resemble antigen-specific memory $CD8^+$ T cells formed during responses to pathogens; thus, all these $CD8^+$ T subsets are long-lived and dependent on IL-7 and IL-15 [15, 25, 56]. Also, MP $CD4^+$ T cells are similar to pathogen-specific memory $CD4^+$ T cells in being dependent on IL-7 (and IL-15) signals [15, 25, 56, 150] (Fig. 3). However, unlike memory $CD8^+$ T cells, the frequency of pathogen-specific memory $CD4^+$ T cells tends to decrease with time [13, 151, 152]. The precise cause of this decline remains unclear.

In contrast to the above-mentioned T cell subsets, $CD4^+$ Tregs rely on IL-2 signals for their homeostatic survival and proliferation. Homeostatic expansion of $CD4^+$ Tregs in lymphopenic hosts is driven by elevated IL-7 levels and probably also depends on paracrine IL-2 signals from activated T cells. Interestingly, it has been suggested that strong IL-15 signals might also impact on Tregs and lead to their expansion [153].

Similar to memory $CD8^+$ T cells, homeostasis of $\gamma\delta$ T cells relies on contact with mainly IL-15 and also IL-7. For NK cells, IL-15 signals are crucial for their homeostatic maintenance under steady-state conditions. Furthermore, increased IL-2 levels are well known to potently activate and expand NK cells.

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