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IL-7 signaling and CD127 receptor regulation in the control of T cell homeostasis

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Summary

After their development in the thymus, mature T cells are maintained in the periphery by two sets of survival signals, namely TCR signals from contact with self-peptide/MHC ligands and the cytokine receptor signals from binding IL-7 and IL-15. These signals cooperate to maximize the utility of finite resources to support a diverse pool of mature T cells. It is becoming increasingly clear that multiple mechanisms exist to regulate expression of IL-7R at the transcriptional and post-translational levels. The interplay between TCR signals and IL-7R signals are also important in regulation of IL-7R expression. This review will focus on regulation of T cell homeostasis by IL-7R signaling, with an emphasis on the cross talk between signals from TCR and IL-7R.

1. Introduction

The overall size and composition of the T cell pool is maintained to be remarkably stable throughout most of the life in normal individuals. The ratio of naïve/memory T cell in the T cell pool is high in the young age, but gradually reverses with age from post-pubescent thymic atrophy combined with life-long immune response to pathogens. The long-term survival of nature T cells is sustained by signals from contact with cytokines and/or peptide/MHC (pMHC) ligands [1, 2]. Indeed, homeostasis of naïve T cells is supported largely by IL-7 and contact with self-pMHC, while memory T cell homeostasis requires only IL-7 and IL-15. These signals maintain naïve T cells in an interphase whereas they induce occasional cell division of memory T cells [3, 4].

During the past decade, IL-7 has been identified as a, if not the, major homeostatic cytokine supporting the survival of various populations of mature T cell, not only for typical $\alpha\beta$ T cells, but also for $\gamma\delta$ T cells, NKT, innate lymphoid cells and even with a partial role for survival of regulatory T cells (Treg). IL-7 is a member of the common gamma-chain (γ_c) cytokine family comprised of IL-2, IL-4, IL-7, IL-15 and IL-21. The receptors (R) for these cytokines share γ_c (CD132) that is associated with a private α chain. An exception exists for IL-2R and IL-15R which are comprised of a third shared β chain (CD122); an additional

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complexity is that IL-15R α is required only for presentation, but not for recognition of IL-15[5]. IL-7R is comprised of a unique α chain (CD127) and CD132. CD127 can also associate with the thymic stromal lymphopoietin receptor (TSLPR), which is not a member of the γ_c family, to bind to TSLP. The normal physiological function of IL-7 was initially discovered as a non-redundant cytokine for B cell and thymic T cell development, and later on for its role in development and survival of most peripheral lymphocyte populations [6, 7]. This review will focus on the role of IL-7 on homeostasis of typical $\alpha\beta$ T cells, as well as the regulation of IL-7 signaling and IL-7R expression.

2. Regulation of T cell homeostasis

It is now broadly accepted that IL-7 is the main cytokine regulating naïve and memory CD4 and CD8 T cell homeostasis and their lymphopenia-induced proliferation (LIP)[2]. LIP defines the capacity of T cells to proliferate when transferred into T cell (T)-deficient hosts, such as irradiated or congenitally T-deficient hosts, due to an increase availability of homeostatic factors [8]. The majority of these studies demonstrated the role of IL-7 on T cell homeostasis by using mice with congenital IL-7 or CD127 deficiency [2]. Due to the importance of IL-7 in T cell development [6, 7], it was difficult to ascertain the role of IL-7 on peripheral T cells in physiologic conditions. Recently, the direct link between peripheral T cell survival and IL-7 in these conditions has been established. In this model, deletion of a T-restricted floxed CD127 transgene in a CD127-deficient background is controlled by an estrogen receptor (ER)-driven Cre recombinase. CD127 deletion induced by tamoxifen-driven ER activation caused a 30% reduction in CD4 and CD8 T cell numbers as rapidly as in 3 days (prior to reduced thymic output), confirming a critical role for IL-7R in maintaining peripheral T cell survival [9]. This model represents a valuable tool to study the importance of sustained IL-7 signals in regulation of memory T cells homeostasis.

Regulatory T cells (Tregs) are important mediators of peripheral tolerance. They develop in the thymus as a distinct T cell population and their survival is mainly dependent on IL-2/IL-2R signaling. However, IL-2 and CD25 deficient mice are not completely devoid of Tregs, as in CD132-deficient mice, suggesting that other γ_c cytokines beside IL-2 participate in Treg development. A role for IL-7, IL-15 and TSLP have been proposed [10–15]. Tregs can also be generated from conventional CD4 T cells *in vivo* or *in vitro* upon T cell stimulation, which are then designated as induced Tregs (iTregs) [16]. In the diabetic NOD mice, adoptive transfer of iTregs can reverse type 1 diabetes (T1D)[17]. Contrarily to natural Tregs, rested iTreg become CD25[−] CD127^{hi}. When transferred into T-deficient mice treated with anti-IL-7 antibodies, the recovery of rested iTreg 10 days post transfer is greatly decreased as compared to control mice. Correlatively, their recovery is increased in CD127-deficient mice, as compared to IL-7 deficient mice, presumably due to accumulation of IL-7 in CD127-deficient mice[17].

To better understand the role of IL-7 in homeostasis of various subsets of T cells, an increasing number of studies are aimed at identifying the mechanism(s) underlying the ability of various T cell subsets to sense and respond to IL-7.

3. IL-7 perception and sensitivity

While both naïve CD4 and CD8 T cell subsets depend on IL-7 for their homeostasis, CD8 T cells are more responsive to IL-7 and undergo a faster rate of LIP than CD4 T cells [18, 19]. This observation raises the question whether IL-7 is differentially available to the two subsets of T cells and/or the two cell subsets possess intrinsically different sensitivity to IL-7. It has been known for some time that stromal cell-derived IL-7 is important for naïve CD8 T cell homeostasis [20]. This stromal cell population has been identified as Gp38⁺CD31[−]CD35[−] fibroblastic reticular cells (FRC), which are localized in the T cell

zones in the secondary lymphoid organs (SLO). IL-7 reporter mice revealed other potential sources of IL-7 T cells in the periphery, like the intestine, liver, skin and lungs [21–26]. However, since LIP depends on access to the SLO [27, 28], IL-7 from the FRCs is most likely the major source of IL-7 supporting T cell homeostasis. Nonetheless, Mack all and colleagues recently reported that IL-7 relevant for CD4 T cells is produced by bone marrow (BM)-derived cells, and more surprisingly, IL-7 from FRC is antagonistic for CD4 T cells [29]. However, the validity of these conclusions have been challenged, as they were based on potential experimental artifacts and also because the conclusions could not be confirmed in other experimental systems [30].

Although availability of homeostatic cytokines is an essential factor regulating T cell homeostasis, increasing evidence demonstrate that T cell intrinsic properties can also account for their sensitivity to homeostatic cytokines. For example, although CD8 T cells respond to IL-15 much better than CD4 T cells, this trait alone cannot account for their differential rates of LIP; this is because CD8 T cells still undergo a faster rate of LIP than CD4 T cell in IL-15-deficient hosts [19, 31]. Recently, the increased sensitivity of naïve CD8 T cells to homeostatic cytokines has been shown to correlate with a higher expression level of monosialotetrahexosylganglioside (GM1)-containing lipid rafts on CD8 than CD4 T cells [32]. This hypersensitivity was observed to IL-2 and IL-15 *in vitro*, required a low-level TCR signal, and was inhibited by lipid raft disruption [32]. Mechanistically, TCR engagement with self-pMHC ligands was proposed to induce the formation of lipid rafts at the plasma membrane, which then promotes the recruitment of cytokine receptors into these lipid arfts. IL-7R enrichment in the lipid rafts was not assessed in this study, but GM1^{hi} naïve CD8 T cells underwent a faster rate of LIP than GM1^{lo} CD8 T cells, suggesting that GM1^{hi} T cells are more sensitive to IL-7. Hence, a difference in lipid rafts expression between naïve CD4 and CD8 T cells could account for differential responsiveness to IL-7 (Fig. 1). Another possibility is that MHC class I (MHC-I) molecules are more ubiquitously expressed than MHC class II (MHC-II) molecules and induce a stronger TCR signaling to CD8 T cells than CD4 T cells, although these two possibilities are not mutually exclusive.

4. IL-7R signaling

4.1. Does IL-7 induce PI3K activity, and is it relevant for T cell homeostasis?

Several studies have shown that IL-7 binding to IL-7R induces rapid activation of the PI3K pathway. However, the majority of the data were obtained from immortalized cell lines, primary thymocytes or recent thymic emigrants. Hence, PI3K activation, as measured by phosphorylation of its downstream target Akt, was found to be indispensable for IL-7 mediated survival and proliferation of neoplastic T cell acute lymphoblastic leukemia [33]. IL-7 was also shown to induce activation of PI3K pathway and proliferation of CD34⁺ subset of human immature CD4[−]8[−] double negative (DN) thymocytes. In contrast, however, IL-7 does not activate PI3K in more mature CD34[−] human thymocytes, which are comprised of CD127[−] double positive (DP) and CD127⁺ or CD127[−] single positive (SP) cells [34, 35]. Since such analyses were not performed with purified subsets of thymocytes, it is difficult to conclude whether the finding is due to the presence of CD127[−] cells or from dissociation of the PI3K pathway from IL-7R.

The recent thymic emigrants (RTE) can undergo homeostatic proliferation in response to elevated doses of IL-7 [36, 37]. Human RTE can also proliferate in response to IL-7 *in vitro*. Such proliferation requires activation of PI3K and PI3K-driven upregulation of glucose transporter Glut-1 [38]. Nonetheless, PI3K activation was found not to be required for survival of RTE supported by low doses of IL-7, which appears to be mediated by activation of STAT5 [38]. These findings suggest that distinct signaling pathways are involved for IL-7-induced survival versus homeostatic proliferation of T cells. Similar notion may also

apply to typical long-lived naïve T cells, although this is yet to be systematically addressed. Nevertheless, this idea is consistent with the finding that Akt phosphorylation in naïve T cells is not detectable with a short-term stimulation with IL-7, but requires prolonged exposure to high concentrations of IL-7 [9, 39, 40]. Furthermore, even stimulation of effector/memory human T cells with a high dose of IL-7 for 1 hour failed to induce strong Akt phosphorylation [41].

The duration and intensity of IL-7R signaling that supports survival and homeostatic proliferation of mature T cells under *in vivo* conditions are unknown. Considering that IL-7 is present in very limited amounts under *in vivo* physiological conditions, together with the fact that IL-7 binding down regulates IL-7R expression, it is unlikely that T cells are continuously stimulated by high concentrations of IL-7. Acknowledging these factors [42], a report recently estimated that low concentration of IL-7 *in vitro* (from 0.01 to 0.1 ng/ml) corresponds to the *in vivo* exposure to IL-7 [43]. Of note, inhibition of PI3K does not affect survival of T cells maintained *in vitro* by such low doses of IL-7 [43]. These studies further suggest that PI3K activation is dispensable for IL-7-induced survival of T cells.

To our knowledge, the issue of whether PI3K activation is essential for IL-7-mediated homeostasis of mature T cells is still far from clear. Class IA PI3K are activated downstream of tyrosine kinase coupled receptors, including TCR and cytokine receptors. These PI3K are composed of a regulatory subunit that is essential to stabilize and bring a catalytic subunit to the plasma membrane, where it phosphorylates the phosphatidyl-(4-5)-biphosphate (PIP2) into phosphatidylinositol-(3-4-5)-triphosphate (PIP3) [44]. Mice deficient in the major Class IA PI3K regulatory subunits possess normal numbers and subsets of peripheral T cells [45]. However, mice with a knock-in recombination in the p110 δ locus leading to the expression of a catalytically inactive form of p110 δ have a decreased CD44^{lo}/CD44^{hi} ratio. Unfortunately, the absolute T cell number in these mice was not been evaluated [46]. Thus, while it is possible that class IA PI3K may regulate naïve T cell homeostasis, much work remains on whether their contribution is mediated downstream of IL-7R and/or TCR.

4.2. IL-7R and Jak/STAT pathway

The most thoroughly described signaling molecules induced downstream of IL-7R are those belonging to the Jak/Stat pathway. The CD127 and γ_c chains are associated to Jak1 and Jak3, respectively [47]. Upon IL-7R triggering by IL-7, Jak1 and Jak3 phosphorylate each other by a mechanism that is yet to be defined [48]. Once phosphorylated, Jak3 can phosphorylate the tyrosine 449 residue of CD127, a motif that specifically recruits the transcription factor STAT5 (a heterodimer of STAT5a and STAT5b). The bound STAT5 is in turn phosphorylated by Jak1 and/or Jak3. STAT5 then translocates into the nucleus and controls expression of target genes involved in survival and proliferation of T cells (reviewed in [49]). It is worth noting that for TSLPR, which forms a heterodimer with CD127 to bind to TSLP, it was recently determined that phosphorylation of STAT5 bound to CD127 is mediated by Jak1 (associated to CD127) and/or Jak2 (associated to TSLPR) [50].

Mice deficient for both STAT5a and STAT5b have a severe combined immunodeficiency phenotype similar to γ_c , CD127 or Jak3 deficiency [51]. Mice with T cell-restricted deletion of STAT5, as well as transgenic mice overexpressing Suppressor of Cytokine Signaling 1 (SOCS1), a negative regulator of cytokine signaling that inactivates all four members of the Jak family, have a strongly reduced numbers of peripheral naïve CD4 and CD8 T cells, demonstrating that STAT5 downstream signals are important for naïve CD4 and CD8 T cell survival [51, 52]. However, the numbers of CD44^{hi} MP T cell populations remain intact in SOCS1 transgenic and T cell-restricted STAT5 deficient mice. The mechanisms by how these MP cells persist have not been determined, but they could be surviving on cytokines

that do not trigger the Jak/STAT pathways and/or from TCR signaling. This notion arises because survival of memory T cells normally requires IL-7 and IL-15, which activate the Jak/STAT5 pathway. An essential role of STAT5 activation in MP T cell survival is also supported by the findings that constitutive STAT5 activation increases the survival of memory precursor and memory CD8 T cells during an LCMV infection [53], and STAT5 deletion during LCMV response curtails the emergence of effector CD8⁺ T cells, but not effector CD4⁺ T cells [54]. However, since STAT5 is activated downstream of multiple cytokines, including IL-2, IL-15 or IL-21, it is difficult to ascertain that these functions are solely mediated by IL-7.

A valuable mouse model to address the role of IL-7R-induced STAT5 activation is the CD127 with Y449F point mutation (CD127^{Y449F}) knock-in mouse, which cannot activate STAT5 downstream of IL-7R [40]. In these mice, the size of the peripheral T cell pool is reduced by 75% as compared to control mice. Much of this reduction is a result of severely depressed thymic development, but impairment of T cell homeostasis also appears to be a significant factor. Hence, when transferred into lymphopenic hosts, both CD4 and CD8 T cells from CD127^{Y449F} mice underwent poor LIP [40]. While failure of STAT5 activation is implicated in this model, one should bear in mind that CD127^{Y449} residue is also important for PI3K recruitment and activation [55], pathway that appears to be involved in IL-7-induced LIP (see previous section). The relative contribution mediated by PI3K vs. STAT5 pathways via CD127 is yet to be defined.

4.3. IL-7 mediated survival mechanisms

IL-7 maintains T cell survival by regulating expression of the B-cell lymphoma 2 (Bcl-2) family of molecules, particularly Bcl-2 and Mcl-1, which inhibit the mitochondrial apoptotic pathway. Experiments in Mcl-1 conditional deficient mice have shown that Mcl-1 is important for thymocyte survival. Indeed, Mcl-1 deficiency induced at the DN stage caused T cell deficiency, as a consequence of thymocyte developmental arrest at the DN3 (CD4⁸-CD25⁺ CD44⁻) stage [56, 57]. This DN3 blockade can be overcome by the deletion of the pro-apoptotic proteins Bak, but not Bax or Bim, showing the specific ability of Mcl-1 to suppress Bak proapoptotic activity [58]. Consequently, T cell development is restored in Mcl-1/Bak double deficient mice. Also, the overexpression of the anti-apoptotic molecule Bcl-2 does not rescue the DN cell differentiation block from Mcl-1 deficiency, showing that Mcl-1, not Bcl-2, is the master regulator of DN thymocyte survival [58]. At the DP stage, deficiency of either Mcl-1 or Bcl-x_L led to only a modest depletion of DP cell survival, whereas double deficiency led to near complete loss of DP thymocytes [56]. Hence, Mcl-1 and Bcl-x_L play partially overlapping roles to support survival of DP thymocytes.

The IL-7-induced signaling pathway involved in survival of thymocytes has been studied in a DN thymocyte cell line D1. In these cells the pro-apoptotic molecule Bad is phosphorylated and inactivated in a PI3K-dependent manner upon IL-7 stimulation [59, 60]. IL-7 withdrawal induces association of Bad to the mitochondria-bound Bcl-2 and consequent induction of apoptosis. Bax, another pro-apoptotic molecule, is also recruited to the mitochondria upon IL-7 withdrawal [59, 60].

One of the main issues with the majority of above studies in terms of mature T cell homeostasis is that a deficiency in an anti-apoptotic molecule often leads to a block in the development of thymocytes. Hence, this thymic defect precludes chances to study the role of these molecules for peripheral T cell survival and only a limited set of studies has been performed. It is likely that many of the molecules important for thymocyte survival are also essential for peripheral T cell persistence. Hence, when Mcl-1 deletion was selectively induced in peripheral T cells under *in vitro* or *in vivo* conditions, the T cell survival was also greatly impaired [56, 57]. In human effector/memory T cells, IL-7 withdrawal induced

apoptosis by downregulating Mcl-1, Bcl-2 and Bcl-xL expression. Moreover, chemical inhibitors of Jak/STAT, but not PI3K, antagonized IL-7-induced upregulation of Mcl-1, Bcl-2 and Bcl-xL [41].

The proapoptotic molecule Bim also appears to have an important role on mature T cell survival, as Bim-deficient mature T cells persisted in greater numbers than wild type T cells upon adoptive transfer into IL-7-deficient hosts [61]. Mechanistically, IL-7 does not seem to regulate expression of Bim, which in T cells is constitutively associated to the mitochondria, poised to execute the terminal stages of apoptosis. Instead, Bim activation is prevented by binding of Mcl-1, which is upregulated by IL-7 [61]. Thus, T cell death appears to be a default pathway, which needs to be suppressed continuously by cytokines that induce expression of anti-apoptotic molecules.

Recent studies challenge the view that IL-7 controls the expression of Mcl-1 and Bcl-2 in peripheral mature T cells. Using different mouse models where the expression of CD127 transgene in a CD127 deficient background can be controlled [62], two studies have shown that induced deletion of CD127 for 3 days had no effect on Bcl-2 and Mcl-1 expression in T cells, therefore suggesting that IL-7 signaling does not regulate expression of these molecules [9, 63]. However, a main caveat here is that half-life of Bcl-2 and/or Mcl-1 could be longer than 3 days. Nonetheless, these inducible CD127 deficiency models should allow clearer studies on whether IL-7 signaling controls Bcl-2 and Mcl-1 expression in mature peripheral T cells under physiological conditions.

It should be emphasized that current understanding on the intracellular mechanisms controlling survival of mature T cells was largely obtained from studies using lymphopenic hosts and *in vitro* treatment with high concentrations of IL-7. Hence, these findings should be reevaluated under physiological conditions [43]. In addition, it may be beneficial to study the promoter regions of Bcl-2 and Mcl-1 to identify binding sites of IL-7-induced transcription factors, such as STAT5. Finally, studies on IL-7-induced post-translational modifications and localization of pro/anti-apoptotic molecules using physiological experimental models may help to bring a better understanding on the mechanisms underlying IL-7-mediated survival of mature T cells. These investigations could also reveal additional mechanisms underlying the differential sensitivity of CD4 and CD8 T cells to IL-7, which is not discernable in experimental condition where IL-7 signals are saturating.

Besides being dependent on balanced pro- and anti-apoptotic signals, resting T cell survival is also dependent on their ability to maintain cellular metabolism, and particularly glucose metabolism [64]. Upon stimulation with growth factors, T cells increase their rate of glucose uptake and glycolysis. It has been known for a long time that IL-7 can prevent atrophy of T cells by promoting glucose metabolism *in vitro* [65]. This important IL-7 function is mediated via the regulation of the cell surface expression of the glucose transporter GLUT1 in a CD127^{Y449}-dependent manner [66]. Thus, the FL5.12 murine pro-B cell lymphoid cell line expressing CD127^{Y449F} failed to uptake glucose upon stimulation with IL-7. Interestingly, GLUT1 regulation occurs mainly at the level of GLUT1 distribution rather than synthesis, because the total cellular GLUT1 expression amount is similar between the wild type and CD127^{Y449} mutant cells. Roles for PI3K and STAT5 have been implicated in this process, but it is not known whether these effectors are mediated downstream of IL-7 or are relevant under *in vivo* physiological conditions of limited IL-7 availability [66]. The use of CD127^{Y449F} mice should allow reliable studies on the role of IL-7 on the glucose metabolism under physiological conditions. Nonetheless, the potent *in vitro* effect of IL-7 to modulate mature T cell surface expression of GLUT1 and glucose uptake is evident even under relatively low concentrations of O₂ found in lymphoid organs that attenuate cell cycle entry [67].

The relevance of IL-7 in controlling glucose metabolism under *in vivo* conditions has only been described recently. As alluded above T cells transferred into IL-7 deficient hosts undergo atrophy and shrink in cell size [65]. In addition, abrogation of CD127 expression on normal mature T cells did not alter the total GLUT1 levels (although cell surface expression was not measured) and glucose uptake, but reduced the rate of glycolysis and led to cell atrophy [9]. These results clearly show that IL-7R signaling through CD127 is important for maintaining T cell metabolism by regulating glycolysis; however, the role of IL-7, and the contribution of the Y449 residue of CD127, on GLUT1 expression and glucose uptake remain to be clarified.

5. CD127 regulation

It has been known for some time that signals induced by both IL-7 and self-pMHC ligands are essential for T cell homeostasis. However, how these two types of signals synergize and/or antagonize to support T cell survival is still unresolved. Besides this TCR/IL-7R crosstalk, an increasing number of molecules regulating expression of IL-7R are being identified.

5.1. Regulation of CD127 expression

The expression level of CD127 dictates T cell sensitivity to IL-7. Because of the limiting amount of IL-7 availability *in vivo*, its consumption is tightly controlled by IL-7-induced downregulation of CD127, presumably in order to maximize the total number of T cells that can be supported by IL-7[42]. In the absence of IL-7 signaling, CD127 expression at the cell surface is regulated by ephrins, which are the ligands of the largest receptor tyrosine kinase receptor family. T cell restricted deletion of Ephrin (Efn) molecules, particularly Efnb1 and Efnb2, is associated with a decreased peripheral naïve T cell compartment size[68]. These Efn interact directly with CD127 and stabilizes CD127 expression on T cells[68] (Fig. 2). Indeed, CD127 downregulation is accelerated in Efnb1/Efnb2 double deficient T cells upon IL-7 stimulation, concomitant with a decreased Stat5 phosphorylation. Also, overexpression of Efnb1 or Efnb2 in EL-4 T cell line is sufficient to delay IL-7-induced downregulation of CD127 in these cells [69]. This enhanced downregulation is linked to a decreased rate of T cell LIP in irradiated hosts [69].

Upon IL-7 stimulation, CD127 expression is downregulated from the cell surface. Although CD127 regulation occurs at the transcriptional level by multiple mechanisms (see below), it is also regulated at the post-translational level. CD127 does not persist stably at the cell surface in the absence of IL-7, but is rather constantly endocytosed via the clathrin coated pits and recycled back to the plasma membrane.[70]. In the absence of IL-7, only a fraction of CD127 is degraded through the proteasomal and lysosomal pathway, with the rest recycled back to the plasma membrane. Upon IL-7 stimulation, the degradation/recycling ratio is inverted in favor of degradation, leading to decreased surface expression of the CD127[70]. This increased degradation is dependent on Jak-3 activity and applies to CD127, but not to the γ_c chain, according to studies with a human lymphoma T cell line [70, 71] (Fig. 2). The recycling of CD127 to the plasma membrane has been shown to depend on the Class III PI3K, Vps34. Vps34 is involved in autophagy, a process that has been shown to be important for T cell survival [72]. Vps34 phosphorylates phosphatidylinositol (PI) into PI-3-phosphate (PI3P) on the membranes of intracellular compartments, promoting the recruitment of FYVE and GLUE domains-containing proteins, which are important for subcellular sorting of internalized molecules [73]. Mice with T cell-restricted Vps34 deficiency have decreased T cell numbers in the thymus and periphery[74]. Although Vps34 associated lymphopenia is not related to a defect in autophagy, Vps34 deficient naïve T cells have decreased cell surface expression of CD127, despite normal total levels of CD127 [74]. This finding suggests that Vps34 controls CD127 recycling/degradation. A

detailed study of the CD127 internalization process showed that Vps34 deficiency leads to a defect in the maturation of the multivesicular bodies (MVB), which emerge from the early endosomes, and are important for the degradation and recycling of internalized receptors (Fig. 2). Therefore, recycling of CD127 to the cell surface fails to occur in Vps34-deficient naïve T cells, and this defect may prevent T cells from receiving IL-7-dependent survival signals[74]. Whether Efnb1 and/or Efnb2 are still associated to CD127 during the recycling process is unknown.

CD127 expression is also regulated at the transcriptional level. For example, it has been demonstrated that activity of Gfi-1 transcriptional repressor and new protein synthesis are involved in CD127 downregulation in CD8 T cells after IL-7 stimulation[42]. During viral infection, the memory-precursor effector cells (MPEC; CD127^{hi} KLRG1^{lo}) regain CD127 expression, as opposed to the short-lived effector cells (SLEC; CD127^{lo} KLRG1^{hi}) [75], thereby making CD127 a marker for memory precursor CD8 T cells. Mechanistically, it has been shown that induction of CD127 expression on effector cells is independent of IL-7 signaling, since CD127^{hi} MPECs can emerge in IL-7 deficient mice infected with VSV [76]. CD127 transcription is inhibited in effector CD8 T cells by recruitment of the histone deacetylase HDAC1 onto the CD127 promoter, allowing further recruitment of the transcriptional repressor Gfi-1 on the CD127 locus. In MPEC, CD127 expression is restored by the recruitment of GABP α , a transcription factor of the Ets family, to the CD127 promoter, and this change correlates with a higher level of histone acetylation of CD127 promoter[77]. These transcription factors have been previously shown to regulate CD127 expression during the steady state, with GABP α promoting and Gfi1 inhibiting CD127 expression, respectively [35, 42, 78, 79]. Accordingly, T cell-restricted Cdc42 deficiency induced increased transcription of Gfi-1 and consequent decreased transcription of CD127 and naïve T cell viability [80]. The Cdc42 phenotype can be reverted by expression of a transgene encoding a constitutively active PAK1, which is directly activated by Cdc42[80]. Correlatively, the expression of a mutant form of Cdc42 incapable of binding PAK1 fails to revert the survival defect and the decreased CD127 expression observed in Cdc42-deficient T cells[80]. This study suggests that Gfi-1 regulates CD127 expression downstream of Cdc42/PAK1 (Fig. 1). Another transcription factor belonging to the Ets family, Ets-1, maintains CD127 expression on naïve and central-memory CD4 and CD8 T cells, and its deficiency greatly reduces naïve CD4 and CD8 T cell numbers *in vivo* [81, 82]. Ets-1 deficient naïve T cells are non-responsive to IL-7 and are impaired in their ability to survive or undergo LIP in lymphopenic hosts[81, 82]. Ets-1 also seems to play a role in survival of antigen-driven T cells, since the maintenance of the fast-dividing donor T cells in RAG-deficient hosts, which proliferate in response to commensal bacteria [83], is decreased over time in the absence of Ets-1 [82].

More recently, additional transcription factors have been shown to regulate CD127 expression. Mice with T cell-restricted deficiency of Foxo1, a transcription factor that is inactivated by the PI3K/Akt signaling pathway downstream of TCR, have a lower number of naïve T cells in the periphery, despite normal thymic T cell development. This has been attributed to a reduced expression of the homing molecules CD62L and CCR7, as well as CD127 on peripheral T cells [84–88]. Moreover, Foxo1 deficient naïve CD4 and CD8 T cells fail to survive and undergo LIP [84, 85]. If PI3K were to be activated downstream of IL-7R, Foxo1 inactivation could be another factor contributing to CD127 downregulation upon IL-7 stimulation.

5.2. CD127 and TCR crosstalk

In lymphopenic MHC-I- or MHC-II-deficient hosts, donor CD8 and CD4 T cells, respectively, are impaired in their ability to undergo LIP. One possible role for TCR signaling could be to enhance T cell responsiveness to IL-7. The mechanism behind how

TCR signaling can tune responsiveness to IL-7 is beginning to be understood. The relative strength of TCR affinity to self-pMHC ligands, which is closely associated with CD5 expression level[89], correlates with the efficiency of naïve T cells to undergo LIP in lymphopenic hosts. Indeed, CD5^{hi} naïve polyclonal T cells proliferate more strongly in lymphopenic hosts than CD5^{lo} naïve T cells [32, 90, 91]. As mentioned earlier, TCR interactions with self-pMHC ligands in naïve CD8 T cells may promote lipid raft formation at the plasma membrane and enhance sensitivity to IL-7[32]. However, whether such enhanced sensitivity to IL-7 is due to increased recruitment of IL-7R into lipid rafts remains to be determined.

IL-7 signaling in turn can tune TCR sensitivity of CD8 T cells through the transcriptional regulation of the coreceptor CD8[92]. Indeed, IL-7 treatment *in vivo* increases CD8 expression on T cells, whereas it is decreased in IL-7 deficient mice. On the other hand, homeostatic TCR signaling provided by self-pMHC ligands in certain conditions can decrease IL-7R signaling, which in turn reduces CD8 expression, thereby maintaining TCR reactivity to self-ligands without inducing overt auto reactivity [92]. These mechanisms may apply only to CD8, but not CD4 T cells, since expression of the CD4 coreceptor is not regulated by IL-7 stimulation[92].

Although homeostatic TCR signaling enhances sensitivity to IL-7, some TCR signaling pathways are known to antagonize IL-7 responsiveness, mainly by downregulating CD127 expression (Fig. 1). For example, RASA1, a RasGAP (Ras GTPase-activating protein) that is activated downstream of TCR, has been shown to influence naïve T cell homeostasis. Activated Ras controls several signaling pathways, including MAPK pathway, with the Erk-2 member being important for survival of antigen-activated T cell [93–95]. RASA1 terminates Ras activation, and its downstream effectors, by inducing Ras GTPase activity. An inducible peripheral T cell-restricted RASA1 deficiency causes a partial loss of CD4 and CD8 naïve T cells. Although activation and LIP of these mutant naïve T cells is normal, RASA1 deficiency reduces naïve T cell sensitivity to IL-7, leading to impaired survival[96]; expression of CD127 in this context has not been evaluated. One could imagine that regulation of Ras by RASA1 upon TCR signaling by self-pMHC ligands finely regulates T cell sensitivity to IL-7, and may participate in the interplay between the CD8 coreceptor and IL-7 signaling discussed above. In lymphopenic conditions, excessive amount of IL-7 could overwhelm this delicate tuning of IL-7 sensitivity by RASA1, resulting in unopposed LIP. An in depth study of TCR signaling pathways triggered upon stimulation by self-pMHC ligands would help to resolve this question.

Survival of activated T cells stimulated by cognate antigens is supported by signals that are different from and supersede those controlling naïve T cell survival at a resting state. Indeed, IL-2 and IL-7 have “opposing” functions; the deficiency in IL-2 causes alymphoproliferative disease as opposed to the inhibition of such a disorder upon neutralization of IL-7 signaling [97]. IL-2 stimulation of activated T cells also antagonizes CD127 expression in a PI3K-dependent manner [98]. As mentioned earlier, Foxo1, whose transcriptional activity is induced in the absence of PI3K/Akt activation, directly promotes CD127 transcription[84, 85]. Another transcription factor of the fork head family, Foxp1, has an opposing role on T cell homeostasis as compared to Foxo1 (Fig. 2). How Foxp1 activity is regulated in T cells is yet to be defined, but naïve CD8 T cells deficient for Foxp1 have increased expression of CD127, which induces homeostatic proliferation *in vitro* or *in vivo* in response to IL-7[99]. Furthermore, Foxp1 compete with Foxo1 for the same DNA binding site in the CD127 enhancer region [99]. In mouse Tregs, Foxp1 expression appears to be dependent on both Foxo1 and Foxo3 [100, 101], but the Foxo1/Foxo3 dependence of Foxp1 expression has not been studied in non-Treg T cells. However, Foxp1 expression remains unchanged in Foxo1 deficient T cells [85], probably reflecting a redundancy between Foxo1 and Foxo3.

Additionally, overexpression of Foxo1 in human T cells is sufficient to induce Foxp1 transcription in a microarray experiment (Carrette F., Fabre S. and Bismuth G. unpublished data) (Fig. 1). It would be interesting to determine the role of Foxos and Foxp1 transcription factors in the steady state. Indeed, while it is clear that the Foxos are inactivated upon stimulation by cognate antigen, their modulation induced by homeostatic TCR and IL-7R signals is largely unknown.

The Src homology domain containing tyrosine phosphatase 2-interacting transmembrane adaptor protein (SIT) is a phosphatase that negatively regulates TCR signaling. In the absence of SIT, there is an accumulation of DP thymocytes, along with a moderately decreased numbers of SP CD4 and SP CD8 thymocytes. Correlatively, the number of mature T cells in the periphery is also moderately decreased [102]. However, there is a strong decrease in naïve peripheral T cell number in the lymph nodes, concomitant with an increase in MP CD8 cell number in the spleen, but this is only observed for CD8, not CD4 T cells. LIP experiments using multiple lines of TCR transgenic CD8 T cells with variable self-pMHC sensitivity have shown that SIT inhibits LIP in T cells with a weak TCR affinity for self-pMHC ligands. Importantly, it seems that IL-7R signaling is not altered in SIT-deficient CD8 T cells, which is surprising given that a crosstalk between TCR and IL-7R signaling maintains T cell homeostasis [103]. However, it is possible that IL-7R signaling in these cells has been assessed using non-physiologically high concentrations of IL-7, thereby masking a role for SIT in responsiveness to physiological concentrations of IL-7. Hence, whether the increased LIP of SIT-deficient T cells is partly mediated by modulation of IL-7R expression and/or signaling is not yet known.

6. Perspectives

A challenge to future investigations will be to determine whether the signaling molecules or transcription factors that regulate CD127 expression also control T cell homeostasis under physiologic conditions. Indeed, these studies often used traditional blunt knock-out approaches that cannot distinguish subtle synergy and cross-talk between IL-7R and TCR. For instance, in human T cells, IL-7 stimulation causes a transient downregulation of CD127, whereas TCR stimulation leads to prolonged suppression of CD127 expression [104]. In addition, a comparative study of the molecules regulating CD127 expression and recycling in CD4 and CD8 T cells may provide better insights into their differential responsiveness to IL-7. New insights into regulation of IL-7R modulation and signaling will also have potential application for cancer biology. This is because it was recently shown that 9% of the T cell acute lymphoblastic leukemia in humans are due to a gain of function mutation in the CD127 locus leading to a constitutive Jak1 activation [105]. Finally, since it is now possible to accurately estimate the IL-7 concentration encountered by T cells under physiological conditions [43], future studies should compare the signaling pathways induced under low and high levels of IL-7 found in normal and lymphopenic conditions, respectively. These studies could bring insight into better the rapies for reconstituting T cells in immunocompromized patients, or to combat cancer driven by a constitutively activated IL-7R signaling pathway.

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Figure 1. Cross-talk between signals from self-pMHC and IL-7

Many transcription factors and molecules downstream of TCR control CD127 expression, either by inducing or inhibiting its transcription. In green; transcription factors inducing CD127 transcription. In red; transcription factors repressing CD127 transcription. TCR signals can also induce formation of lipid rafts, which could recruit and concentrate IL-7R, thereby amplifying its downstream signaling pathway. It is still unclear if IL-7 signaling activates the PI3K signaling pathway in lymphoreplete hosts, but if it were to be true, Foxo1 and Foxp1 could finely regulate CD127 expression downstream of IL-7, allowing a limited IL-7 to support survival of a maximal number of T cells. Whether Gfi-1, GABP α or Ets-1 are activated downstream of IL-7R or self-pMHC/TCR interactions is still not known, but Gfi-1 expression is induced downstream of strong TCR triggering [79, 80, 106].

Figure 2. IL-7-induced recycling/degradation of CD127

In the absence of IL-7, the ephrins Efnb1 and Efnb2 stabilize CD127 expression at the cell surface. Eventually, CD127 will be internalized. Vps34 activity in the multivesicular bodies will recruit FYVE and GLUE containing proteins that will allow the recycling of a significant proportion of the CD127 chain back to the cell surface. Upon IL-7 binding to the IL-7R, the internalized receptor is targeted to the lysosomal and proteasomal degradation pathways in a Jak3-dependent manner. The Vps34-dependent recycling does not apply to the γ_c chain, which is always degraded by the lysosomal pathway