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The Many Faces of IL-7: From Lymphopoiesis to Peripheral T Cell Maintenance

Terry J. Fry and Crystal L. Mackall

IL-7 is well known as a lymphopoietic cytokine, but recent studies have also identified a critical role for IL-7 in peripheral T cell homeostasis. IL-7 is well poised to serve as a homeostatic cytokine because it is produced by resting stromal cells, the IL-7R is present on most T cells, and IL-7 down-regulates its own receptor. These features allow IL-7 to signal large numbers of resting T cells and to be efficiently used when supplies are limiting. Consistent with this, in normal hosts, IL-7 is required for survival of naive T cell populations, and IL-7 contributes to homeostatic cycling of naive and memory cells. In addition, lymphopenic hosts accumulate increased levels of IL-7, and the supranormal levels are largely responsible for inducing homeostatic peripheral expansion in response to lymphopenia. Thus, IL-7 plays critical and nonredundant roles in both T cell lymphopoiesis and in maintaining and restoring peripheral T cell homeostasis. The Journal of Immunology, 2005, 174: 6571–6576.

Interleukin-7 was discovered in 1988 as a result of its growth-promoting effects on B cell progenitors in vitro (1). During the ensuing decade, much of IL-7 research focused on lymphopoiesis where it plays a critical role. More recently, however, a central role for IL-7 in peripheral T cell homeostasis has also emerged. This review will summarize current understanding of the role IL-7 plays in lymphocyte development and then discuss in more depth the emerging role that IL-7 is assuming as a modulator of peripheral T cell homeostasis. IL-7 is well known as a lymphopoietic cytokine, but recent studies have also identified a critical role for IL-7 in peripheral T cell homeostasis. IL-7 is well poised to serve as a homeostatic cytokine because it is produced by resting stromal cells, the IL-7R is present on most T cells, and IL-7 down-regulates its own receptor. These features allow IL-7 to signal large numbers of resting T cells and to be efficiently used when supplies are limiting. Consistent with this, in normal hosts, IL-7 is required for survival of naive T cell populations, and IL-7 contributes to homeostatic cycling of naive and memory cells. In addition, lymphopenic hosts accumulate increased levels of IL-7, and the supranormal levels are largely responsible for inducing homeostatic peripheral expansion in response to lymphopenia. Thus, IL-7 plays critical and nonredundant roles in both T cell lymphopoiesis and in maintaining and restoring peripheral T cell homeostasis. The Journal of Immunology, 2005, 174: 6571–6576.

The unique, nonredundant role for IL-7 in murine B and T cell development is most clearly demonstrated by the paucity of lymphocytes present in IL-7- and IL-7Rα-deficient mice and following IL-7 or IL-7Rα neutralization in vivo. The subsequent description of patients with T− B− NK− SCID resulting from an IL-7Rα chain mutation confirmed that IL-7 is essential for human T cell lymphopoiesis. However, because these patients had B cells expressing the mutant IL-7R, these results demonstrated that IL-7 is not absolutely required for B cell development in humans (2). Nonetheless, it is likely that, under normal circumstances, IL-7 signaling contributes substantially to the efficient generation of the human B cell repertoire (3).

The effects of IL-7 on T cell lymphopoiesis are multiple and distinct for different lineages at different stages of differentiation. In some cases, such as in γδ TCR rearrangement, the effect of IL-7 is indispensable, because γδ cells are completely absent from IL-7−/− mice. At other steps in T cell development, IL-7 plays a primary role under normal circumstances, but the effects can be rescued by other elements when IL-7 is limiting. For example, TSLP can substitute, albeit suboptimally, for IL-7 in thymopoiesis, and likely serves as the basis for less T cell deficiency in IL-7−/− compared with IL-7Rα−/− mice (4).

During lymphocyte development, IL-7Rα is first expressed on the common lymphoid progenitor (CLP) in the bone marrow, a cell initially considered to be the requisite progenitor for both T and B cell lymphopoiesis (5). The observation that CLPs expressed IL-7Rα led to the initial assumption that IL-7 signaling was sustained throughout the early steps in lymphopoiesis; however, recent evidence has indicated that IL-7Rα subsets also represent important stages in B cell and T cell development. One example is the recent description of the earliest T lineage progenitors within the thymus, which do not express

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2 Abbreviations used in this paper: γδ, common γ chain; TSLP, thymic stromal lymphopoietin; CLP, common lymphoid progenitor; DN, double negative; HPE, homeostatic peripheral expansion; RTE, recent thymic emigrant.
IL-7Rα, yet efficiently generate T cells (6, 7). Furthermore, although the IL-7Rα+/CLP preferentially gives rise to B cell progenitors (8, 9), sustained expression of IL-7Rα chain in lymphoid progenitors impairs B cell development (10). Finally, CD34+ CD38+ CD7+ lymphoid progenitor identified in human cord blood also lacks IL-7Rα (11). Therefore, whereas some early lymphoid progenitors can be identified by IL-7Rα expression, this is not universal and strict regulation of IL-7Rα expression appears to be a common and important theme in lymphopoiesis.

Beyond the earliest T lineage progenitor stage of thymopoiesis, IL-7 is critical for the differentiation of double-negative (DN) thymocytes. IL-7 is a potent growth factor for DN thymocytes, likely serving as an amplification step in thymopoiesis. In addition, because T cell development in IL-7- or IL-7Rα-deficient mice can be partially rescued by a becl-2 transgene or deletion of Bax, IL-7′s capacity to prevent cell death contributes substantially to effects on thymopoiesis (12–14). Recent data demonstrated that both survival and proliferative effects generated through IL-7Rα via PI3K in DN thymocytes are required primarily to overcome inhibitory signals rendered by phosphatase and tensin homologue deleted on chromosome 10, because mice deficient in this factor can efficiently generate T cells in the absence of IL-7 (15). In addition to survival and proliferative effects, IL-7 also plays a direct role in inducing γ-chain rearrangement by augmenting histone acetylation and locus accessibility (16) and also contributes to β-chain rearrangement (17).

At the DN3 stage of T cell development, signals generated by a productively rearranged β-chain and pTα (pre-TCR) serve to maintain IL-7Rα expression, perhaps allowing responsiveness to limiting concentrations of IL-7 and successful transition to the DN4 stage (18). A similar mechanism for maintaining IL-7Rα expression has been proposed for pre-BCR signaling (19). However, sensitivity to IL-7 is lost at the intermediate single-positive stage, and forced IL-7Rα expression inhibits the transcription factors necessary for progression to the double-positive phase resulting in a blockade in T cell development (20). Munitic et al. (21) have demonstrated that the forced expression of IL-7Rα beyond the DN stage also results in diminished size of the DN pool, and have suggested that this may occur as a result of IL-7 consumption, which results in a reduced supply of IL-7 available for DN thymocytes. Thus, during early T cell development, IL-7 signals are critical for survival, proliferation, and gene rearrangement in thymocytes, but loss of IL-7Rα expression allows normal T cell development to proceed and, perhaps, maintains an adequate DN pool size. Regulation of IL-7Rα also plays an important role during the double-positive stage of development because IL-7Rα re-expression is important for CD8+ lineage commitment (22, 23), an effect that may be regulated, in part, by the transcriptional repressor, GFI1b (24). Furthermore, Van De Wiele et al. (25) have reported that, based on patterns of STAT-5 phosphorylation, the responsiveness of human thymocytes to IL-7 was at least partially regained in thymocytes involved in the positive selection process.

The voluminous evidence that IL-7 is an indispensable element in normal thymopoiesis raised the intriguing possibility that diminished IL-7 production could be responsible for age-associated thymic involution and/or that IL-7 therapy may enhance thymopoiesis in lymphopenic patients or in aging individuals. Whereas this was an attractive hypothesis pursued by many laboratories, studies thus far have not provided convincing evidence that age-associated thymic involution is due to diminished IL-7 production (26), and in general, increasing IL-7 availability has not increased thymic size or thymic throughput. Included in this body of work are a number of studies of IL-7 transgenic mice that show contrasting phenotypes in the thymus, ranging from unaffected to, perhaps surprisingly, decreased thymic cellularity. A recent report suggested that a dose effect was an important element in these distinctions with the highest levels of IL-7 inducing diminished thymic size (27). This observation is supported by the diminished thymic size of nonhuman primates treated with pharmacologic doses of IL-7 (28). Furthermore, treatment of aged mice with IL-7 did not reverse histologic evidence of thymic involution (29). One exception may involve irradiation-based preparative regimens for bone marrow transplantation, wherein some reports have demonstrated that IL-7 therapy may accelerate recovery of thymic function (30), perhaps because the IL-7-producing epithelial cells appear to be particularly sensitive to the effects of radiation (31). Therefore, although IL-7 therapy may hold promise for clinical application as an immunoregenerative (discussed below), current evidence does not support the notion that IL-7 therapy, per se, increases thymic size and thymic throughput, or is capable of preventing or reversing thymic involution.

**IL-7 and peripheral T cell homeostasis**

Early reports identified IL-7′s capacity to costimulate for TCR activation in mature T cells, but because animals lacking IL-7 had negligible numbers of peripheral T cells, the central role for IL-7 in peripheral T cell homeostasis remained largely underappreciated. However, several studies in the last 5 years have established IL-7 as a critical modulator of peripheral T cell homeostasis, the effects of which are most pronounced during T cell lymphopenia. Although an exhaustive review of the literature describing alterations in T cell physiology during lymphopenia is beyond the scope of this article (reviewed in Ref. 32), several points relevant in the context of IL-7 will be discussed.

Due to some of the ambiguity associated with terminology in the current literature, clear definitions are necessary. Homeostatic peripheral expansion (HPE) can be defined as the dramatic mitotic expansion of mature T cells occurring in lymphopenic hosts. The fact that mature T cells expand in lymphopenic environments has been appreciated for over 20 years (33), but the mechanisms have only recently been elucidated. Some investigators have also used the term “HPE” to describe the slow cycling of naive cells and/or the ongoing cycling of memory cells that occurs throughout life. Although these phenomena may represent a continuum, the extent and rate of cell turnover in T cell-replete vs lymphopenic animals differ substantially. Therefore, we prefer to use the term “homeostatic cycling” to describe the turnover of naive or memory cells, which 1) occurs in lymphoreplete hosts, 2) does not clearly result in expansion of cell numbers, and 3) does not alter the naive vs memory phenotype or functional profile of the cycling population. In contrast, “HPE” will be used to describe expansion that 1) occurs in lymphopenic hosts, 2) results in dramatic expansion of cell numbers, and 3) for naive cells, results in a conversion to a memory phenotype. It is now evident that HPE, as it occurs in lymphopenic hosts, results in full conversion to a memory phenotype (34, 35), and that gene expression induced following HPE is similar to that induced by encounter with cognate Ag (36). Whether memory cells generated via HPE...
share all of the functional characteristics of memory cells generated in response to cognate Ag remains an unresolved question. Indeed, genes related to cytolytic function seem to be expressed to greater extent on cells encountering cognate Ag when compared with cells undergoing HPE (36). Nonetheless, distinguishing between homeostatic cycling as it occurs in lymphoreplete hosts and HPE that occurs in lymphopenic hosts is useful for illustrating the contribution of IL-7 in modulating peripheral T cell homeostasis.

Homeostatic cycling and survival of naive cells/recent thymic emigrants (RTEs)

Following thymic export, RTEs are preferentially incorporated into the periphery regardless of the size of the existing pool (37). Once in the periphery, RTEs continue to undergo differentiation and cycling. Although fully mature thymocytes generally show low IL-7Rα expression, Bourjalous et al. (38) reported increasing expression of IL-7Rα following thymic export, with preferential peripheral expansion of the IL-7RαhighCD8+ subset. Similarly, human cord blood T cells show enhanced responsiveness to IL-7 compared with adult naive T cell populations, and neonatal T cells, which are largely comprised of RTEs, demonstrate a high turnover rate and heightened responsiveness to IL-7 (39, 40). Thus, cycling of RTEs, which contributes to efficient postthymic T cell differentiation and maintenance of a diverse T cell repertoire, is highly correlated with IL-7 responsiveness. Furthermore, when IL-7 is administered to normal nonhuman primates, the percentage of cycling cells in the blood increases dramatically (41), with the most profound changes in the naive subset (42). Thus, exogenous administration of IL-7 is sufficient to induce widespread cycling of naive T populations in primates and RTEs in cord blood. In addition, IL-7 may also contribute to trafficking of RTEs to lymphoid tissues (43). Although Ag is not absolutely required for IL-7-induced cycling of RTEs, it appears likely that TCR signaling via cross-reactive environmental and/or low-affinity self-Ags is involved in much of the naive cell cycling induced by IL-7. Indeed, when exogenous IL-7 is administered with a cellular vaccin, IL-7-mediated expansion of Ag-specific T cell populations is much greater than the expansion of non-Ag-specific populations, thus demonstrating the synergy of concomitant TCR and IL-7 signaling (44). The adjuvant effect of IL-7 is most dramatic on subdominant Ags, wherein coadministration of IL-7 can dramatically augment effector cell generation (44).

Once RTEs are integrated into the naive peripheral pool of a T cell-replete host, they enter a resting phase characterized by no or very slow proliferation. Such quiescent cells nonetheless can dramatically augment effector cell generation (44). The adjuvant effect of IL-7 is most dramatic on subdominant Ags, wherein coadministration of IL-7 can dramatically augment effector cell generation (44).

Adoptive transfer of naive T cells into lymphopenic animals results in dramatic expansion via the process defined above as HPE. A variety of studies have confirmed that TCR signaling is critical for HPE. Indeed, when cognate Ag is available to T cells in the setting of lymphopenia, the magnitude of expansion induced exceeds that found in T cell-replete hosts responding to the same Ag (35), and the magnitude of expansion in response to cognate Ag exceeds that recently described to occur in response toward Ags with lower affinities for the TCR (55, 56). Thus, T cell repertoires generated during the process of HPE tend to be oligoclonal and skewed toward dominant Ags (35), a feature currently being exploited in the context of immunotherapy.

In addition to the exaggerated response to cognate Ag, there is also a fundamental change in the nature of the Ags capable of inducing proliferative T cell responses during lymphopenia. Goldrath and Bevan (55) and Ernst et al. (57) definitively demonstrated that HPE involves the proliferation of T cells toward Ags with low affinity for the TCR and which therefore represent both self-Ags responsible for positive selection in the thymus and low-affinity cross-reactive environmental Ags (55, 57, 58). Subsequently, Schluns et al. (59) and Tan et al. (60) demonstrated that IL-7 is required for the proliferation of naive cells to low-affinity Ags during HPE, whereas IL-15, IL-4, and other cytokines tested were not required. Importantly, the features of HPE and the role for IL-7 appears largely consistent regardless of the method by which lymphopenia is induced, including HPE of CD4+ T cells in normal lymphopenic neonatal mice (61–63). Therefore, the contribution of IL-7 to HPE is not a trivial effect of irradiation or other exogenous environmental factors but rather reflects a central requirement for IL-7 in the induction of HPE.
possible that other factors present during lymphopenia contribute to HPE, the discrepancies regarding the effect of IL-7 have most commonly involved a subset of cells that undergo very rapid proliferation despite IL-7 neutralization in lymphopenic hosts. Indeed, CFSE dilution studies by several groups have consistently demonstrated the requirement for IL-7 for the slower proliferation characteristic of response to low-affinity Ags. However, in many of these reports, IL-7 neutralization has had little effect on the most rapidly proliferating pool contributing to HPE. We have interpreted this to mean that proliferative responses resulting from high-affinity interactions (e.g., cognate Ag driven) are those that are least dependent upon IL-7, whereas the contribution of low-affinity T cells to HPE critically depends upon IL-7.

Modulating peripheral T cell homeostasis via IL-7: the dosage effect

In general, cytokine receptor signaling is modulated primarily at the level of receptor expression, and IL-7 is no exception in this regard. What is exceptional about IL-7R when compared with other cytokine receptors, is the high expression of IL-7R on naive CD4+ and CD8+ resting T cells, with slightly higher levels on neonatal CD4+ T cells (RTEs). Whereas other γδ cytokine receptors are up-regulated following T cell activation, expression of IL-7Rα is lost on effector cells, but then re-expressed on memory cells. Furthermore, whereas γδ cytokines typically induce their respective receptor expression, IL-7 down-regulates expression of IL-7Rα on CD8+ T cells through activation of the transcriptional repressor, GFI1 (64). IL-7Rα down-regulation contributes to maintenance of the size of peripheral T cell pool, because IL-7Rα transgenic mice, which are unable to down-regulate the receptor, show diminished peripheral T cell numbers (64). Thus, IL-7Rα expression is tightly regulated on peripheral T cells in a manner resulting in efficient use of this limiting resource; most resting cells express IL-7Rα, which allows them to receive basal IL-7 signals for survival and proliferation; however, the cells down-regulate IL-7Rα following IL-7 signaling or activation.

As described above, a role for IL-7 has been demonstrated in both naive cell survival and homeostatic cycling, which occurs in T cell-replete hosts, as well as in HPE, which occurs in response to lymphopenia. These studies have generally evaluated each process in the presence vs absence of IL-7 either through Ab neutralization or by using mice genetically manipulated so that they either cannot produce or respond to IL-7. Despite the insights that these studies provide, they have not clarified why the combination of TCR signaling and IL-7 induces survival and at most, minimal cycling without phenotypic or functional changes of naive cells in T cell-replete hosts, whereas the same combination induces dramatic expansion of naive cells and conversion to a memory phenotype in lymphopenic hosts. Whereas non-IL-7-related changes in lymphopenic hosts such as deletion of regulatory cells could contribute, we have postulated that a dosage effect of IL-7 (65),
resulting from increasing availability of this cytokine as lymphopenia progresses, plays a critical role in distinguishing “homeostatic cycling” in lymphoreplete hosts from “HPE,” which occurs in lymphopenic hosts. The dosage effect model of IL-7 holds that progressive lymphopenia leads to diminished IL-7 use with a resultant increased availability of IL-7, thus allowing proliferation to lower and lower affinity TCR interactions (Fig. 1).

Indeed, in conditions of severe lymphopenia, IL-7 appears capable of inducing proliferation independent of TCR signals (66). Although this model supports direct effects of IL-7 on T cells as a central component modulating the outcome of interaction between T cells and low-affinity Ags, other factors such as the IL-7-induced modulation of APCs could also contribute. Indeed, TSLP, which shares the IL-7Rα chain has been shown to modulate CD4+ HPE via dendritic cell effects (67), and we have observed IL-7 signaling on APCs as a critical component of its effects in vivo (68).

The most illustrative insights into the role that lymphopenia plays in altering IL-7 availability have come from human studies. Several groups have demonstrated that CD4+ lymphopenia in humans is associated with reciprocal increases in circulating IL-7 (69–71). Normally, young children maintain IL-7 levels of 10–20 pg/ml, whereas healthy adults maintain IL-7 levels of 2–8 pg/ml. However, IL-7 levels gradually rise with progressive CD4+ lymphopenia to levels as high as 60 pg/ml. Increases in serum IL-7 levels in clinical settings associated with lymphopenia have been described in bone marrow transplantation, HIV infection, chemotherapy treatment for cancer, and idiopathic CD4 lymphopenia. Although inordinately low levels of IL-7 in infection, chemotherapy treatment for cancer, and idiopathic CD4+ lymphopenia have been described in bone marrow transplantation, HIV infection, chemotherapy treatment for cancer, and idiopathic CD4 lymphopenia, several groups have demonstrated that CD4+ plays in altering IL-7 availability have come from human studies (68).

IL-7 levels appear to have a diminished capacity for immune reconstitution, a result that implies that increased IL-7 contributes to the restoration of T cell homeostasis (72, 73). Interestingly, IL-7 levels have been most tightly correlated with CD4+ counts wherein the IL-7 level reproducibly declines upon CD4+ recovery. In contrast, CD8+ recovery and even CD8+ expansions have not been associated with declines in circulating IL-7 levels, a result that suggests that IL-7 levels may be regulated primarily by CD4+ T cell mass. Although the increased IL-7 levels could result from increased production, emerging data from murine studies have demonstrated that lymphopenia is associated with decreased rather than increased production of IL-7 (C. L. Mackall, unpublished observations). Thus, we currently favor a model wherein IL-7 accumulates in settings of CD4+ lymphopenia due to diminished use, similar to the pattern of regulation observed with other hemopoietic cytokines that serve to maintain homeostasis of target cell populations (e.g., thrombopoietin, G-CSF). Whether the dose-response effect of IL-7 relates to a capacity for higher cytokine concentration to signal cells with lower receptor levels, whether higher IL-7 levels lead to altered intracellular signaling pathways, or whether alternative IL-7R expressing populations contribute remains an issue for further study. Nonetheless, it appears clear that the increased availability of IL-7 present in lymphopenic humans is a critical factor modulating the T cell physiology induced in this setting.

Potential therapeutic applications for IL-7

Clinical development of IL-7 is currently underway. The most obvious application for this cytokine is to enhance immune reconstitution during lymphopenia. As discussed above, whereas true increases in thymic throughput will likely play a minor role in the clinical effects of IL-7 therapy, it is predicted that IL-7 will increase cycling of RTEs, which could provide important benefits for patients with profound T cell depletion. This may be especially important in the setting of T cell-depleted allogeneic stem cell transplantation, where diminished immune reconstitution remains a primary roadblock to progress. In addition, the capacity for IL-7 to augment responses to weak or low-affinity Ags raises the possibility that IL-7 may be useful as a vaccine adjuvant, especially when weak Ags, such as tumor Ags, may be targeted. IL-7 is also predicted to enhance the effectiveness of adoptive immunotherapy through its capacity to augment memory cell memory cycling. In addition to beneficial immunostimulatory effects, elevated levels of IL-7 may also contribute to autoimmunity or to proliferation of neoplastic lymphoid cells. If so, then approaches to neutralize this agent and/or to prevent the increases induced during T cell depletion could provide a clinical benefit.

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