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IL-7: the global builder of the innate lymphoid network and beyond, one niche at a time

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Abstract

The development and homeostasis of adaptive and innate lymphocytes is dependent on the stromal cytokine IL-7. The initial priming of immune responses to pathogenic challenges is executed by innate lymphoid cells (ILCs) with programmed capacity to rapidly secrete effector cytokines. How ILCs are controlled by IL-7 in distinct anatomical locale has evolved into a more complex problem as IL-7 receptor is not only expressed on ILCs, but also on surrounding neighbors, including vascular endothelium and mesenchymal cells that compete for limiting IL-7. For the generation of γδ T and B cells IL-7 is required for the production of antigen receptors, and it is likely that IL-7 performs critical function in facilitating ILC effector programming in addition to its regulatory actions on cell survival and proliferation. Most of our current understanding of the highly calibrated regulatory circuits of IL-7 function and IL-7 receptor signaling has derived from studies of adaptive, conventional lymphocytes. Here we highlight recent advances in mapping the gene circuits and cellular interactions that regulate temporospatial activities of IL-7 in diverse macro and micro niches that have direct relevance to deciphering the sphere of impact of IL-7 on ILC differentiation.

Keywords

Innate lymphoid cells; IL-7 reporter mice; T cell development; gammadelta T cells; gut associated lymphoid tissues; regulation of IL-7R expression

1. Introduction

Homeostasis is the necessary poised state for adaptations to constantly changing environments in biologic systems. The immune system's basal set point is established by a vast array of regulators and reinforcing molecular circuits often tailored with exquisite cell type-specificity. Disturbances of the set point can lead to hyperstasis or disease states and a suboptimal functioning network of sensors tuned to environmental variations. The gene encoding for the cytokine IL-7 was identified 24 years ago [1], and since then, intensive research has established IL-7 as the prototypic regulator of lymphocyte homeostasis. IL-7 controls the birth (as a precursor maintenance factor and a permissive factor of TCRγ and Ig

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gene rearrangement and expression, [2,3]), education (as a $CD8^+$ thymocyte selection tuner [4]), persistence (as a tonic stimulator outside the thymus [5]), maturation (as a system memory promoter [6,7]) and death (as a pro survival factor [8]) of T cells. Several insightful reviews have been published recently on IL-7 function in lymphocyte development and maintenance [9-11]. In this review, we focus on the emerging details on the developmentally regulated spatial distribution of IL-7 in vivo that controls all IL-7 receptor (IL-7R) expressing cell subsets with tissue specific and systemic functions in immunity, with a particular emphasis on innate lymphoid cells (ILCs).

ILCs can be broadly classified into two subtypes based on their origin: the primary lymphoid tissue-derived γδ T, αβ NKT, innate $CD8^+$ αβ T, mucosa associated invariant T cells (MAITs), NK and B-1 cells [12,13], and the gut-associated lymphoid tissue (GALT)-derived Lymphoid Tissue initiator (LTi)-related subsets programmed to produce the Th17 signature cytokines, IL-17 and IL-22 (ILC17 and ILC22), and Th2 cytokines IL-5 and IL-13 (ILC5/13) [14]. As exemplified by innate γδ T effector subsets that mirror the repertoire of adaptive $CD4^+$ T effector subsets (Th1, Th2 and Th17) [15], ILCs are the first responders to environmental insults and as such their effector lineages are programmed in tissues they originate, eliminating the time consuming acquisition of “learned” effector capacity upon pathogen encounter. IL-7 is one of the earliest cytokines consumed by developing ILCs in all anatomical sites where they originate and it has the capacity to program lineage specific gene expression, including the gene circuits that specify the effector identity.

2. In vivo sources of IL-7

Without IL-7 the lymphoid system cannot be built. In rodents, IL-7 is the only cytokine absolutely critical for the generation of innate (γδ T, αβ NKT) and adaptive (αβ T and B) lymphocytes in the primary lymphoid tissues (thymus and bone marrow, BM). In the gut, ILCs capable of IL-17 and IL-22 production express IL-7R and are dependent on IL-7 for their generation [16,17]. In the secondary lymphoid tissues, IL-7 is required for the maintenance of naïve lymphocytes (αβ T and B cells) along with tonic signals transmitted by clonal antigen receptors. While IL-7 has a similar functional profile in humans, B cells are not absolutely beholden to IL-7 for development and survival. For innate lymphocytes (NKT, γδ T and NK cells) and memory T cells that have an activated phenotype and express IL-2Rβ, a component of the high affinity IL-15R, IL-15 is the companion factor of IL-7 that can replace the need for antigen receptor-mediated signals [18-21].

IL-7 is predominantly produced by stromal and vascular endothelial cells, with very low levels of *Il7* transcripts detectable in adult animals, consistent with the concept that under basal states there are limited amounts of IL-7 available for lymphocytes *in vivo* [22]. Stroma-derived IL-7 production can be induced by severe alterations in the environment, such as hypocellularity induced by radiation damage [23] and overt inflammation [24], but in a homeostatic animal the amount of IL-7 produced is thought to be constant. Analyses of five different IL-7 genetic reporter mice have been published (reviewed in [25]). These mice have provided broadly similar results regarding IL-7 expression, with higher levels of IL-7 in sites of lymphopoiesis, including the BM and thymus, than in peripheral lymphoid tissues. Using transgenic mice containing a BAC substrate with Cre knocked into the first exon of the IL-7 locus, we have tracked in detail cells that have expressed IL-7 at some point during their life and/or continue to express it [26]. Analysis of IL-7promoter-Cre $Rosa26^{eYFP}$ reporter mice showed that IL-7 is expressed by specialized lymphoid stromal subsets in BM, lymph node (LN), liver, Peyer's patches (PP), isolated lymphoid follicles, a subset of intestinal epithelium, thymic epithelial cells, specialized vascular endothelium and dermal fibroblasts.

Classically, cytokines and chemokines were assumed to operate with free diffusion characteristics, leading to a protein gradient within the localized microenvironment to which cells respond. However, IL-7 binds strongly to heparin sulfate proteoglycans (HSPGs) in the extracellular matrix (EM) *in vivo* and does not form a linear gradient from cellular factories. HSPGs on both stromal cells and lymphocytes have key roles in regulating IL-7/IL-7R interactions [27], with the amount of bio-available IL-7 controlled by a combination factors: IL-7 production rate and half-life, production and secretion of soluble IL-7R (sIL-7R), IL-7 binding kinetics to HSPGs, rates of EM deposition by stromal cells and EM degradation by MMPs, interaction properties between IL-7R$^+$ cells and the EM, and IL-7R levels on non-haematopoietic cells in the local microenvironment. Different lymphoid microenvironments, including the thymus, BM and secondary lymphoid tissues, have variable EM composition and HSPG expression patterns, resulting in a finely tuned and complex regulation of IL-7 bio-availability and attendant localized competition among IL-7R$^+$ cells. Unbound IL-7 is found at very low levels in blood serum, thus posing a challenge to its detection in tissues in experimental or clinical settings. Changes to IL-7 levels in serum have been shown to be a predictive biomarker of cardiovascular diseases. This correlation may relate to changes to the EM in vessels associated with cardiovascular disease or localized IL-7 production from inflamed tertiary lymphoid tissue formation associated with atherosclerotic plaques [28]. In contrast, higher relative amounts of sIL-7R to membrane IL-7R are causally linked to T cell mediated autoimmune diseases such as Multiple Sclerosis [29]. Similarly, lower levels of bio-available IL-7 are found in HIV infection, potentially caused by increased levels of sIL-7R detectable in serum samples. The increased sIL-7R levels did not, however, correlate with either viral load or the size of CD4$^+$ T cell population [30]. sIL-7R predominates in lung tissues, perhaps indicating a differential role for sIL-7R in a local microenvironment-specific manner [31]. These data collectively suggest that IL-7 has a diverse functional profile in different localized microenvironments, with roles in both the maintenance and regulation of tissue specific lymphocyte populations and in the development and function of tissues (see below), but the specific dynamics of IL-7 activities in localized microenvironments have not been precisely measured.

3. IL-7R signaling

The IL-7R is composed of the common γ (γc) chain and a unique α chain. IL-7 exhibits a decisive preference for the glycosylated form of IL-7R, and docks onto it using a distinctive two-step binding mode [32]. The α chain of the IL-7R is also utilized by Thymic Stromal Lymphopoietin (TSLP) while the γ chain is the shared component of the cytokine receptors for IL-2, IL-4, IL-9, IL-15 and IL-21, all with essential functions in T effector subset differentiation and maintenance. γc cytokines activate the JAK-STAT pathway and IL-7R and other cytokine receptor signaling has also been shown to engage PI3 Kinase (PI3K) and mTOR pathways [33,34]. The unique activities of each γc cytokine can in part be accounted for by the combinatorial utilization of distinct JAKs, STATs and PI3K stimulation in a cell type-specific manner [34,35]. IL-7Rα recruits JAK1 while phosphorylated γc associates with JAK3. JAKs in close proximity cross-phosphorylate each other, leading to signal amplification. In addition, the IL-7/IL-7R complex partitions into lipid rafts and associates with active JAKs and STATs as well as cytoskeletal proteins [36], suggesting that membrane fluidity may be another parameter distinguishing γc associated receptors and their signaling capacity. TSLP binds to the IL7Rα in complex with the TSLP receptor (encoded by *Crlf2*) and can partly compensate for the absence of IL-7R signaling in vivo, despite the fact that it does not strongly activate the JAK3-STAT5 pathway, instead recruiting JAK2 for its signaling [37,38].

3.1. Regulators of IL-7R signaling

Suppressors of cytokine signaling (SOCS) proteins are a family of E3 ubiquitin ligases that inhibit cytokine induced intracellular signals by direct interaction with components of various cytokine receptors, aborting kinase activity and targeting receptor associated kinases such as JAKs and the receptors themselves for degradation [39]. For IL-7, SOCS1 is the major negative regulator of signaling expressed in most phases of developing T and B lymphocytes, tuning sensitivity to γc cytokines. Ectopic over expression of SOCS1 in developing thymocytes phenocopies mice lacking γc or Jak3 [40], and physiological levels of SOCS1, while permissive for IL-7R signaling in T cells, are dynamically regulated. T cell development in the absence of SOCS1 is characterized by hyper IL-7 and IL-15 signaling, primarily impacting the generation of $CD8^+$ cytotoxic T cells with an activated phenotype [41].

While SOCS proteins are induced by a variety of cytokines and thought to function in a negative auto-feedback loop, SOCS1 expression in developing lymphocytes may be less critically dependent on cytokines. IL-7 has not been reported to induce SOCS1 in developing thymocytes. Rather, the transcription factor (TF) Zbtb17 (Miz1), expressed in most lymphoid cells throughout development (Immgen.org), has been shown to regulate IL-7R signaling through direct modulation of *Socs1* expression [42,43]. Canonical WNT signaling components might also be a significant regulator, as enforced expression of a stabilized β-catenin transactivator that results in TCF1 activation in T cells led to increased IL-7R expression and signaling, and a coincident downregulation of SOCS1. Conversely, in thymocytes lacking β-catenin, SOCS1 was upregulated, leading to impaired thymocyte development [44].

That the amount and/or duration of IL-7R signaling is tightly calibrated is further illustrated by the observation that additional E3 ubiquitin ligases and a deubiquitinase (DUB) directly and indirectly control IL-7R expression levels: T cells in mice lacking c-Cbl, a negative regulator of TCR signaling and AKT amongst other activities, are endowed with higher IL-7R expression and are hyper responsive to IL-7 in vitro [45]. Innate-like invariant $Vα14^+$ NKT cells (*i*NKT) lacking the CYLD DUB are prone to apoptosis correlating with decreased IL-7Rα expression as a result of hyperactive NκKb signaling [46]. The reduced IL-7R signaling leads to decreased expression of ICOS, which is necessary for NKT cell homeostasis. These findings not only reveal a Byzantine network of proteins that modulate the IL-7R signaling pathway depending on activation states of the cells, but also attest to the calibration of normal IL-7R signaling to a tight range of active regulators.

3.2. Factors controlling IL-7R expression in lymphocytes

One central characteristic of IL-7R expression is its dynamic regulation by cytokines and by the overall metabolic and differentiation state of the cells. For example, TNFα can upregulate IL-7Rα expression [47], whereas most other trophic cytokines of the γc and gp130 family repress its expression [48]. At basal states, IL-7R expression is relatively high, as exemplified by B and T cell progenitors (e.g., $IL\text{-}7R^+$ clonogenic lymphoid progenitors and $IL\text{-}7R^+C\text{-}kit^+CD25^+CD44^+CD4^-CD8^-CD3^-$ proT cells) and resting naïve lymphocytes in secondary lymphoid tissues. Downregulation of IL-7R expression is a necessary step in early B cell differentiation from progenitors [3,49]. Excessive IL-7 elicited signals are detrimental to the expression of B cell lineage TFs EBF and Pax5 as well as Forkhead box O1 (FOXO1) that induces *Rag1/2* expression [50,51]. Given that EBF, E2A and FOXO1 coordinately impose B cell lineage specification [52], modulation of IL-7R signaling can be considered as a permissive, but not necessarily deterministic [7,49,53], parameter for cell lineage commitment. The apparent paradox that IL-7R signaling is necessary for regulated B cell receptor (BCR) gene rearrangement and expression [3,54], but also dampens the

expression of FOXO1 that turns on *Rag1/2* can be resolved by invoking developmentally compartmentalized IL-7R signaling output. In T and B progenitors, the IL-7R-JAK3-STAT5 circuit dominates and primes the chromatin for transcription and rearrangement in conjunction with cofactors, such as E proteins that are also direct targets of IL-7R signaling [55]. Concurrently, the FOXO1-*Rag1/2* circuit is dampened by the PI3K-AKT (or possibly MAPK) pathway activated by IL-7R in B cells until the proper chromatin state is established [50,51]. With the decline of IL-7R expression and signaling that accompanies maturation, lineage specific factors are induced that selectively propagate cell type-specific chromatin states permissive for gene rearrangement and transcription as well as TFs such as FOXO1 that promotes the expression of enzymes that act on the modified chromatin to generate lineage-specific proteins.

A dynamic modulation of IL-7R signaling necessary for normal differentiation is also evident in the thymus [53,56]. Generation of innate γδ T cells from proT cells is linked to IL-7R expression with IL-7R^{hi} proT cells as the preferred source of γδ T cells relative to IL-7R^{lo} proT cells. Conversely, IL-7R^{lo} proT cells are biased to differentiate into αβ T cells. This bias can be uncoupled from the possible enhancement of TCRγ gene rearrangement/expression in IL-7R^{hi} proT cells as the provision of a rearranged functional TCRγ transgene to proT cells did not alter the observed bias [57]. While the γδ T cell lineage specific TF SOX13 [58] has been suggested to be a positive regulator of IL-7R expression [59], developing immature γδ T cell subsets distinguished based on Vγ chain usage exhibit a range of *Sox13* expression, with the subset containing the highest amount of *Sox13* transcripts expressing the lowest amount of IL-7R on the cell surface (Immgen.org; unpublished). Hence, the link between IL-7R signaling and γδ T cell differentiation remains unclear, exacerbated by more recent findings that different γδ cell subsets may originate asynchronously from multiple developmental intermediates. That distinct IL-7R expression pattern of γδ cell subsets is molecularly linked to the timing of γδ subset generation and serves as a marker of origin rather than function *per se* is currently being investigated. In this setting γδ subsets arising from the earliest T cell progenitors would inherit gene expression programs distinct from those arising from more mature T lineage-committed precursors, including distinct IL-7 sensitivity and effector function programming.

In contrast to developing innate γδ cell subsets that mostly maintain IL-7R expression, adaptive αβ T cell lineage committed precursor thymocytes (C-kit^{lo}CD25^{+}CD44^{-} CD4^{-}CD8^{-}CD3^{-} preT) rapidly lose IL-7R expression, only to regain it after the final steps of maturation prior to thymic egress. For developing αβ T cells, the shutdown of IL-7R expression coincides with the induction of TCR expression, making the cells switch from cytokines for survival to becoming highly focused on preTCR and peptide-MHC complexes for terminal maturation towards the CD4^{+} or CD8^{+} T cell lineages. Another consequence of the selective shut down of IL-7R expression is that the vast majority of thymocytes (αβTCR^{lo}CD4^{+}CD8^{+}) do not consume IL-7, thus permitting limiting local depots of IL-7 to sustain precursor cells, γδ thymocytes (IL-7R$^{mid\text{-}high}$) and selected αβ CD4^{+} and CD8^{+} thymocytes and promote functional maturation [48]. This exclusivity of consumption to highly segregated subsets imparts distinct, tightly regulated differentiation programs to those cells, such as induction of early cell lineage factors (e.g., E proteins) in the progenitors, facilitation of antigen receptor rearrangements and expression for developing cells, and survival of thymocytes that passed developmental checkpoints. A similar dynamic of IL-7R expression occurs in secondary lymphoid tissues such that antigen activated lymphocytes variably lose IL-7R expression, only to resurface on antigen-experienced cells of the memory compartment. It has been suggested that this downregulation is necessary for the democratization of lymphocytes to ensure that the cells that best compete for limiting IL-7 do not dominate [60].

During development, *Il7r* transcription in thymocytes requires GABPα [61], which is a member of the ETS family of TFs, and c-Myb [62], whereas in immature B cells, the ETS TF PU.1 is an additional cofactor for *Il7r* expression [63]. In positively selected $CD4^+$ thymocytes and peripheral $CD4^+$ T cells, RUNX1 activates *Il7r* transcription [64], with ETS-1 acting as a coactivator in both naïve and central memory $CD4^+$ and $CD8^+$ T cells [65]. Growth factor independence-1 (Gfi-1), on the other hand, is the best-characterized repressor of *Il7r* transcription in T cells [48]. In $CD8^+$ effector T cells Gfi-1 is expressed highly and antagonizes GABPa binding to, and modification of, the *Il7r* genomic locus [66]. In peripheral T cells *Gfi* is turned on by low level ERK-dependent antigen receptor signaling [67] and by IL-7 itself (in $CD8^+$ T cells, [48]) thereby establishing an auto inhibitory feedback loop. Conversely, TGFβ downmodulates *Gfi1* expression [68]. In thymocytes, the absence [69] or over-expression of *Gfi1* does not lead to altered expression of IL-7R per cell [70], but rather results in increased apoptosis, particularly of early progenitors

Upon egress from the thymus, the homeostasis of naïve αβ T cells requires tonic cytokine and TCR signals as the cells cruise the secondary lymphoid organs, directed by chemokines and endothelial migratory cues. Trophic signals and cell trafficking behaviors are coordinately regulated by the FOX family of TFs. FOXO TFs in particular have emerged as the central nuclear effectors programming the adaptation of diverse cell types to external variations impacting metabolism and stress [71]. Among lymphocytes, *Il7r* is a direct target of FOXO1 in T, but not B, cells and the absence of *Foxo1* results in decreased *Il7r* expression and the subsequent loss of naïve T cells [60,72]. Concurrently, FOXO1 controls the expression of the primary migratory molecules S1P1, CCR7 and CD62L by directly modulating the TF KLF2 that globally dictates naïve T cell migratory patterns [73]. Cell-extrinsic stimuli of the PI3K-AKT pathway, including TCR ligands, costimulatory B7 molecules that bind to CD28, and pro-survival cytokines such as IL-7, can downregulate molecules of T cell homeostasis by inactivating FOXO1 [50,51]. In naïve $CD8^+$ T cells, FOXP1 is a counter regulator of FOXO1 and therefore an inhibitor of IL-7Rα expression, most likely by direct competition with FOXO1 for docking onto *Il7r* locus [74] In precursor thymocytes FOXO1 expression is low to negligible (Immgen.org), suggesting that this pathway is not a regulatory loop for IL-7R expression during T cell development. As discussed previously, FOXO1 is a B cell lineage specification factor operating in conjunction with E2A and EBF proteins to induce *Rag1/2* expression downstream of IL-7R signaling [50-52]. Whether an auto feedback circular loop consisting of IL-7R and homeostasis regulating FOX family TFs is a general phenomenon in extrathymically-derived ILCs remains to be established.

4. Innate lymphoid cells expressing IL-7R in the gut

Recently, unconventional $IL\text{-}7R^+$ lymphocytes have gained prominence, including ILCs that are prevalent in the gut-associated lymphoid tissues (GALTs). While their functional relevance is just beginning to emerge, recent findings that they are the source of IL-17 and IL-22 inflammatory/regulatory cytokines and thus impact inflammatory set points and control intestinal homeostasis have elevated their immunological stature [14]. In common with other lymphocytes, IL-7R expression is the key feature of GALT ILCs and their developmental programming and acquisition of effector capacity are regulated by genetic circuits that are critical for thymic ILCs, such as Notch-HES1 and TCF1 ([75,76] and unpublished). The founding subset of intestinal ILCs are the Lymphoid Tissue initiator cells (LTis), first identified in the fetal intestine, and essential for PP and LN organogenesis via the production of Lymphotoxins (LT, see below)[77].

4.1. GALT effector ILCs

Two LTi related ILC subsets are ILC22 (also called NK22, NKp46$^+$ in mice, NKp44$^+$CD56$^+$ in humans) and ILC17 (Thy1$^+$, Ly6a (Sca-1)$^+$, IL-23R$^+$). These cells are required for maintaining homeostasis in the gut during inflammatory responses through the rapid production of IL-22, a key mediator of innate responses in gut epithelial cells against bacterial pathogens, and IL-17, which drives pro-inflammatory responses through the localized induction of inflammatory cytokines and neutrophil recruitment [78-80]. All of these subsets are dependent on IL-7 for their differentiation and survival [16,17]. The effector cytokine producers LTi, ILC17 and ILC22 cells are also commonly marked by the expression of RORγt and Id2. RORγt is the central molecule responsible for production of the signature cytokine IL-17 and mice lacking RORγt lack all effector ILCs in the GALTs [81] and peripheral IL-17 producing *i*NKT (NKT17) and γδ T cells (Tγδ17) [76,82-84]. Id2 is an inhibitor of the HLH E protein TFs that are also expressed by non-GALT associated ILCs, including IL-7R$^+$ NK progenitors in the BM, NK cells, *i*NKT cells and innate CD8$^+$ T cells [12,13,85-87]. Although IL-7 has been implicated as a permissive factor for GALT ILC effector cytokine production [88], the molecular link between RORγt/Id2 expression and IL-7 has not been established. In fact, the co-expression of IL-7R and the signature ILC defining TFs is somewhat counterintuitive. Two well characterized TFs, STAT3 and IRF4, induce RORγδt transcription [89,90], but neither is primarily regulated by IL-7. In conventional CD4$^+$ T cells, IL-2 activated STAT5, the primary STAT of IL-7R signaling, is a negative regulator of *Rorc* [91]. Further, in developing thymocytes, IL-7R signaling is not permissive for *Rorc* expression [56]. IL-7R signaling is also necessary for E protein induction in lymphoid precursors [55] and it seems unlikely that a direct link exists between IL-7 and Id2. Clearly, regulation of *Rorc* expression in ILCs is distinct from that of conventional adaptive T cells [17], also evidenced by the abundant expression of IL-7R by RORγt$^+$ Tγδ17 cells upon thymic maturation (unpublished), and a role for IL-7 in modulating effector cytokine production in ILCs, if any, will require further studies. Th2-like ILC subsets, which are mostly RORγt-independent, but Id2-dependent, are found in the BM and secondary lymphoid tissues in mice [92,93] and represent innate sources of IL-5 and IL-13 that are necessary for immunity against worms. These ILC5/13 subsets are IL-25 (IL-17e) and IL-33-dependent for expansion, capable of γc chain signaling [94], and express the IL-7R. A similar functional subset is also found in fat cells of the mouse peritoneal cavity [95] and in humans (Crth2$^+$CD161$^+$CD7$^+$CD3$^-$ innate lymphocytes), where they are localized in blood, lung, gut and inflamed nasal tracts [96]. The impact of IL-7R signaling for the members of the ILC5/13 subset has not been studied in detail. IL-7R is also necessary for intestinal enterocytes mediating repair of chemically damaged intestinal epithelial layers. In this inflammatory setting, autocrine TSLP acting on IECs is necessary to induce secretory leukocyte peptidase inhibitor, a tissue repair factor that antagonizes proteases [97,98]. Thus, IL-7R signaling elicited by IL-7 and TSLP in ILCs and stromal cells, respectively, are critical for regulating inflammatory responses in the gut.

4.2. IL-7R signaling-dependent lymphoid organogenesis and maintenance

Cytokines and chemokines not only have key roles in directing lymphocyte trafficking to tissues, but they are essential for organogenesis and maintenance of tissue architecture. For the latter processes, while morphogens dominate in embryogenesis, the IL-7/IL-7R axis along with Lymphotoxins (LTs) and other TNF family of cytokines are the central factors in adult hematopoietic tissue development and organization. IL-7R signaling in LTi (LTα1β2CD45$^+$CD4$^+$CD3$^-$c-Kit$^+$RANK$^+$CCR7$^+$CXCR5$^+$) cells modulates their turnover in developing anlagen [99], as well as inducing CD30L [100] and LTs [77,101]. In humans, LTi cells differ phenotypically, as they do not express CD4, but do respond to IL-7 and are localized to developing LNs [102]. LTi cells persist in adult lymphoid tissues including Tonsils, LNs, intestinal crypotpatches, isolated lymphoid follicles and spleen.

Lymphoid tissues develop as a result of stochastic interactions between IL-7R^{hi} LTi cells and mesenchymal organizer cells (LTo). *In vitro,* IL-7 drives the rapid proliferation of LTi cells and is required for their maintenance. *In vivo,* however, LTi cells in the mid-gut are G0/G1 growth arrested and do not depend on IL-7R signaling for their survival [103](Fig 1.). Rather, IL-7R signaling likely modulates LTi cell responses to chemotactic gradients (IL-7 is not in itself directly chemoattractive [104]), and perhaps most importantly, induces LTp [77,101]. In mice over-expressing IL-7 and TSLP, LTi cell numbers are enhanced and additional ectopic lymphoid tissues develop [37,98,105], confirming that supra-physiological amounts of IL-7 and TSLP can drive LTi expansion *in vivo.* However, in normal mice, this process is not dependent on either IL-7 or TSLP, since no major impairment in PP formation is observed in IL-7 or TSLP deficient mice [98,106] (Fig. 1). It has been previously speculated that an unknown cytokine signals through IL-7R in a JAK3 dependent pathway and has an essential role in PP formation [107], potentially adding further complexity to IL-7R signaling in organogenesis in the GALT.

IL-7R signaling has an important role in LN development and maturation, but LNs can develop in IL-7R-deficient mice using RANK signaling [101]. RANKL is relatively abundant in LN anlagen, but not in GALTs. Exogenous IL-7 infused into RANKL-deficient mice is sufficient for the early phases of LN genesis, but proper compartmentalization within LNs requires the RANKL-TRAF6 signaling pathway. The selective redundancy in LN development may in part results from differences in both the kinetics and numbers of LTi cells and factors necessary for LTi-LTo interactions present in developing LN vs PP anlagen, with all relevant factors particularly limiting in PP. Compound CXCL13, the chemoattractant for LTi cells, and IL-7R-deficient mice lack nearly all peripheral LNs, correlating with a severe reduction in LTi cell numbers in developing LN anlagen [99]. While the provision of IL-7R^{+} T and thymic NK cells can restore neonatal LN genesis in IL-7R or γc chain-deficient mice [108], an increased pool of LTi cells in the absence of other lymphocytes can also be curative [98]. Overexpression of TSLP has been shown to drive the expansion in LTi cells in IL-7 deficient background [37,105]. A common quantitative modifier in all these models may be the increased LTβ that has direct stimulatory effects on stromal LTo of LNs.

5. IL-7R signaling in non-haematopoietic cells

Outside of lymphoid cells IL-7R is expressed on blood and lymphatic vascular endothelial cells, dermal fibroblasts and LN and BM stromal cells, albeit at lower levels than found on haematopoietic cells. Functional IL-7R is also found at low levels on a variety of primary human endothelial cell lines [109]. Stimulation of human aortic endothelial cells with IL-7 leads to a rapid increase in E-selectin, ICAM-1, and VCAM-1 in a PI3K-dependent manner, and MCP-1 through a JAK/STAT-dependent pathway [28]. The up-regulation of these factors in turn modulates the migration of monocytes and macrophages to atherosclerotic lesions *in vivo*. IL-7R is also expressed on breast and lung cancer epithelial cell lines, and stimulation of these cells by IL-7 leads to up regulation of VEGF-D expression. Analysis of tumor biopsies shows a strong correlation between IL-7R expression in the tumor microenvironment, VEGF-D expression and survival probability [110]. While the precise connection between IL-7 and tumorigenesis in vivo has not been established, the VEGF regulated angiogenesis is clearly a potential target of IL-7 that will impact tumor growth and metastasis. Analysis of IL-7p-Cre Rosa26^{eYFP} reporter mice indicates that IL-7 is expressed at some stage(s) of normal mouse breast epithelium differentiation [26]. IL-7 is expressed at physiologically active concentrations in human breast milk, with the levels correlating with thymic function in newborn children and nutritional input from the mothers [111]. Analysis of IL-7 in maternal milk in mice shows that it can cross the intestinal barrier and modulate T cell development in neonatal mice [112]. These results collectively suggest that IL-7R

signaling is functionally relevant for non-haematopoietic cells, particularly in the regulation of vascular network.

6. IL-7 production and IL-7R signaling in bone and liver macro- and microenvironment

Our analyses of IL-7R expression patterns on non-lymphoid cells show expression in diverse human BM stromal populations including multi-potent mesenchymal stem cells and BM stromal cells. In the BM, the mesenchymal stroma directs the development of hematopoietic cells. Examination of stromal subpopulations has shown that Nestin^{+} mesenchymal cells express IL-7 and form niches required for the maintenance of haematopoietic stem cells [113]. Further analysis of the IL-7 expressing BM stroma niches show that these vascular associated microenvironments are required for the first stage (pro-B/pre-BI cells) in B cell development, but subsequent stages of B cell development (pre-BII) occur in IL-7 negative stromal niches expressing Galectin I [114]. Although our understanding of the functional relevance of IL-7R signaling in stromal cells is rudimentary, the effects of IL-7 stimulation in distinct stromal cell lines *in vitro* have provided some leads. Using a BM stromal line that supports *in vitro* cobblestone formation arising from co-cultures of hematopoietic stem cells and stroma, it has been shown that IL-7 induces a ten-fold increase in IL-6 expression [115]. The beneficial effects of in vivo IL-7 administration in boosting immunity to chronic viral infection have been shown to be also dependent on IL-6 [116], suggesting that this inflammatory cytokine may yet emerge as a critical effector of IL-7R signaling in diverse biological settings.

In pathological rheumatoid arthritis (RA), a destructive bone joint disease, high levels of IL-7 in serum have been found to correlate strongly with disease progression [117,118]. IL-7 production is similarly increased in postmenopausal bone as a result of estrogen (E2) loss. High levels of IL-7 in the bone microenvironment have been linked to the loss of bone mass in both RA and E2 through the stimulation of osteoclast formation resulting from the downregulation of OPG, a negative regulator of the RANK/RANK-L pathway [119]. Thus, IL-7R signaling may have a key role in regulating bone remodeling.

As alluded to earlier, IL-7 is expressed robustly in fetal liver and is necessary for the development of lymphoid precursors and LTi during late stages of fetal ontogeny. In the adult liver, sinusoidal endothelial cells express IL-7, FLT3 and SCF and thus have the potential to both maintain the homeostasis of liver resident T cell populations and facilitate B cell development. Co-culture of primary liver sinusoidal endothelium with BM precursor cells (lineage marker negative) led to robust B cell differentiation [120]. Although IL-7 is normally a homeostatic cytokine whose bioavailability is primarily controlled by consumption, administration of LPS into mice leads to the induction of IL-7 in both kidney and liver, dependent on the TRIF-IFNα pathway [24]. This acute induction of IL-7 is likely to have a profound influence in regulating resident liver T cells, including innate iNKT and γδ NKT cells [121], early in the immune response.

7. Perspective

Manipulation of IL-7 remains a viable option to restore homeostasis post trauma, to treat immune diseases such as Multiple Sclerosis genetically linked to *Il7* [122], and to induce temporary hyperstasis to counter damaging environmental insults and cellular transformation [10]. Advances in the basic mechanistic understanding of the shared IL-7 function in the development and homeostasis of innate and adaptive lymphocytes are permitting rationale forays toward clinical applications of IL-7 modulatory strategies to treat chronic viral infection [116], immunodeficiencies [123] and autoimmune diseases [124], and

to improve vaccine efficacy [125]. The pleiotropic effects of IL-7 on the ever-expanding list of IL-7R-expressing cell types, especially outside the adaptive lymphocyte compartment, complicates targeted applications of exogenous IL-7 and modulatory biologicals specific for the IL-7/IL-7R complex. Fine mapping of the gene circuits controlling *Il7* transcription in a context-dependent manner is necessary to improve our understanding of the regulation of localized production of IL-7 and its impact on macro and micro niches. Detailed characterization of cell type-specific IL-7R signaling properties, their dynamic integration with other concurrent signals regulating homeostasis locally and system-wide, and the identification of novel downstream gene targets and their function will permit more selective immunotherapies designed to impact specific IL-7-regulated cellular niches of innate and adaptive immunity.

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Highlights

>We discuss newly emerging details on the regulation of IL-7R expression. >IL-7 regulates the differentiation of all innate lymphoid cells in diverse tissues. >IL-7 may be a permissive factor for arming innate effectors. >Complex competition for IL-7 by multiple cell types in a given niche is addressed.

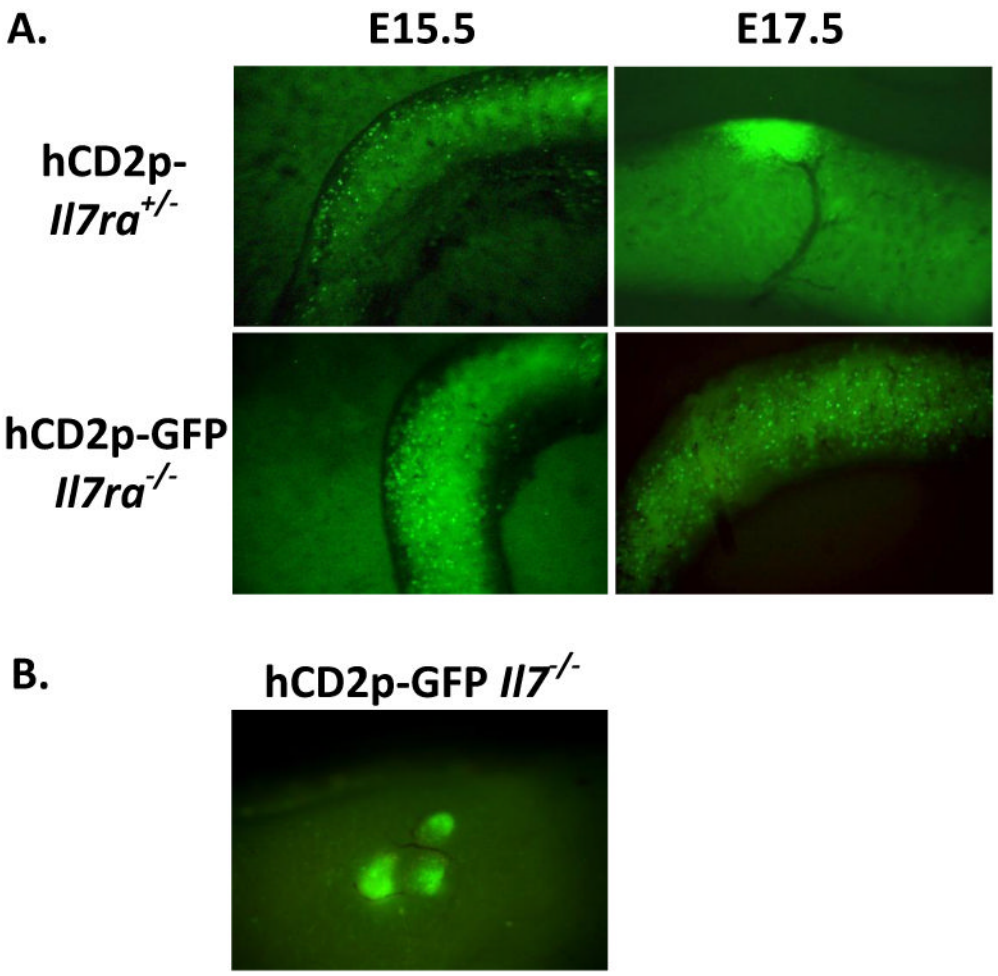

Fig. 1.

To determine the role of IL-7/IL-7R interactions in the development of Peyer's patches (PP) the human CD2 promoter–GFP reporter (GFP^{hi} LTi cells and T cells) transgene expressing *Il7ra*$^{-/-}$ and *Il7*$^{-/-}$ mice were generated and their fetal intestines examined by fluorescent stereo-microscopy (Zeiss M2Bio) for GFP reporter expressing cells to track ILC and T cells. **(A)** No PP were observed in E17.5 *Il7ra*$^{-/-}$ embryos (right panels, PP shown as a concentrated mound of GFP^{+} cells in *Il7r*$^{+/-}$ intestine) or in adult mice (data not shown). Normal numbers of LTi cells were however observed in the mid-gut at E15.5 (left panels). **(B)** In contrast to *Il7ra*$^{-/-}$ mice, development of PP occurred normally in *Il7*$^{-/-}$ mice. Adult PP in *Il7*$^{-/-}$ mice are shown.