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Functions of IL-15 in Anti-Viral Immunity: Multiplicity and Variety

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Abstract

An effective immune response to an invading viral pathogen requires the combined actions of both innate and adaptive immune cells. For example, NK cells and cytotoxic CD8 T cells are capable of the direct engagement of infected cells and the mediation of antiviral responses. Both NK and CD8 T cells depend on common gamma chain (γ c) cytokine signals for their development and homeostasis. The γ c cytokine IL-15 is very well characterized for its role in promoting the development and homeostasis of NK cells and CD8 T cells, but emerging literature suggests that IL-15 mediates the anti-viral responses of these cell populations during an active immune response. Both NK cells and CD8 T cells must become activated, migrate to sites of infection, survive at those sites, and expand in order to maximally exert effector functions, and IL-15 can modulate each of these processes. This review focuses on the functions of IL-15 in the regulation of multiple aspects of NK and CD8 T cell biology, investigates the mechanisms by which IL-15 may exert such diverse functions, and discusses how these different facets of IL-15 biology may be therapeutically exploited to combat viral diseases.

Keywords

IL-15; Anti-viral Immunity; NK Cells; CD8 T Cells; Immune Intervention; Cytokine Therapy

1. Introduction

Cytokines are low molecular weight proteins that mediate intra and intercellular communications in the body. Though most cell types in the body express cytokines or their receptors, a large role for cytokine signaling has been defined in the immune system, and cytokines are best characterized as immunomodulators. As such, cytokine production, regulation, and administration shape the development of the immune response to pathogens, autoimmune disorders, inflammatory diseases, and immunodeficiencies. Within and outside the immune system, cytokines are expressed by a variety of cell types and exert a wide range of functions, often exhibiting a high degree of pleiotropy and redundancy in their effects. This redundancy can, in part, be explained by the sharing of receptor subunits. An often-referred to example is the common gamma chain family of cytokines, which includes IL-2,

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IL-15 has been implicated in the development and immunobiology of both NK and CD8 T cells. Virally induced IL-15 influences the migration and effector function of NK and CD8 T cells. IL-15 has great potential for modulating anti-viral immune responses and vaccine development.

IL-4, IL-7, IL-15, IL-9, and IL-21 and all have multimeric receptors that utilize the common gamma chain (γ_c).

IL-15 is a γ_c cytokine independently identified by two groups in 1994 based on its ability to stimulate the proliferation of the murine T cell line CTLL-2 [1-3]. Now, human, murine, bovine, porcine, feline, and rabbit IL-15 have all been cloned with 70-80% structural homology [4]. Like IL-2, IL-15 is a 14-15 kDa glycoprotein member of the four α -helix bundle-containing cytokines [2, 5, 6]. Additionally, both cytokines signal through trimeric receptors that utilize γ_c , and CD122 (IL-2 R β) [2, 7]. Specificity for a cytokine is conferred to each receptor by a private α chain, CD25 or IL-15R α for IL-2 and IL-15, respectively [8, 9]. IL-15 may be presented in trans to responsive cells expressing CD122 and CD132 by cells expressing the cytokine itself bound to a membrane form of the receptor alpha chain [10], and a similar mode of signaling may also exist for IL-2 [11]. With so many shared structural and signaling components, it is not surprising that IL-2 and IL-15 also share many functional redundancies including induced proliferation of NK and CD8 T cells and enhanced CTL activity in these cell types [12-14]. Both cytokines also induce the proliferation and differentiation of stimulated human B cells [15]. Despite the many overlapping functions between IL-2 and IL-15, however, it has become abundantly clear that IL-15 exclusively mediates many immune functions. Whereas IL-2 has a critical role in activation-induced cell death (AICD), IL-15 appears to always oppose AICD by acting to prolong the survival of T lymphocytes [16, 17]. IL-15 is also exceptional in its ability to support the homeostasis of natural killer (NK cells) and memory phenotype and antigen-specific memory CD8 T cells, and it is probably best characterized for its role in maintaining memory pools of CD8 T cells [18]. Therefore, despite the high degree of redundancy in cytokine signaling within the immune system, IL-15 clearly mediates many important unique aspects of immunity.

Emerging literature is revealing many divergent functions for IL-15 outside of the immune system as well, but many of these functions—and mechanisms by which these functions are differentiated in various cell types—are not well understood. IL-15 transcripts are abundantly expressed in placenta and skeletal muscle, and IL-15 has been implicated in a variety of physiological processes including angiogenesis [19], skeletal muscle hypertrophy [20], endometrial decidualization [21], permeability of the blood brain barrier [22], and body fat composition [23]. IL-15 expression in all tissues is heavily regulated at the posttranscriptional level [24, 25] (Tagaya [26] and Budagian [4]) review these modifications at length). Overall, IL-15 translation is very inefficient due to multiple layers of negative regulation. Such abundant regulatory mechanisms may reflect on IL-15's potency as a pro-inflammatory cytokine. Unchecked IL-15 expression could easily lead to a various inflammatory and autoimmune disorders, and indeed, IL-15 is implicated in the pathology of many of these diseases including inflammatory bowel disorder, celiac disease, and rheumatoid arthritis [27]. However, IL-15 expression induced by an infectious agent is a very important part of transforming NK cells, CD8 T cells, and other cells of the immune system into functional effectors capable of efficiently eliminating pathogens. Both innate and adaptive immune responses can be ramped up or dampened down by increasing or decreasing IL-15 availability, respectively. While it is clear that IL-15 mediates an incredible number of various functions within and outside of the immune system, this review seeks to emphasize the many roles IL-15 plays in modulating immune responses to viral pathogens.

An effective immune response to an invading viral pathogen invasion consists of the combined effects of both innate and adaptive immune cells, which are responsible for the recognition and removal of infected host cells in order to halt viral replication. The cell types best capable of engaging infected cells directly and mediate antiviral responses

through cytokine release (such as IFN γ) are NK cells, lymphocytes of the innate immune system, and cytotoxic CD8 T cells, lymphocytes of the adaptive immune system. As recently reviewed by Sun and Lanier [28], these cell populations bear many parallels to one another, including their professional killing capacities via release of perforin and granzymes, their development from common lymphoid progenitors, and notably, their dependence on γ c cytokine signals for their development and homeostasis. Both NK cells and CD8 T cells must become activated in the presence of foreign antigens, migrate to sites of infection, and be able to survive and expand in order to maximally exert effector functions. Although a variety of cytokine signals are important in this process, IL-15 is a potent activator, chemotactic agent, and homeostatic signal for NK cells and CD8 T cells. This review focuses on the functions of IL-15 in the regulating multiple aspects of NK and CD8 T cell biology, as well as the mechanisms by which IL-15 may exert such diverse functions, and discusses how these different facets of IL-15 biology may be therapeutically exploited to combat virus-mediated diseases.

2. IL-15 and Immune Cell Function

2.1 IL-15 and Natural Killer Cells

In addition to B and T cells, NK cells constitute the third population of cell types that originate from a common lymphoid progenitor. Despite their lymphocyte origin, NK cells have been classified as innate immune cells because they do not use recombination-activating gene (RAG) enzymes to generate specific antigen receptors, and, as such, are able to respond rapidly to infected cells without any prior sensitization [28]. Although IL-15 is an important modulator of many different functions of innate immune cells such as neutrophils, basophils, and eosinophils, NK cells are perhaps the innate immune effector most dependent on IL-15 signaling for development, homeostasis, and function (Fig 1).

All stages of developing NK cells express high levels of CD122, suggesting that IL-15 could act on these cells throughout the entire course of their development [29]. Accordingly, analyses of IL-15^{-/-} and IL-15R α ^{-/-} animals revealed severe reductions in numbers of NK cells, implicating an important role for IL-15 in the development of NK cells [29-32]. The earliest NK cell progenitor does not have any known lineage-specific markers, but is currently identified as a non-stromal bone marrow cell that expresses CD122 and IL-15R α [33]. The necessary expression of CD122 and IL-15R α by NK cell progenitors highlights how important IL-15 signaling is in the early development of NK Cells, and *in vitro* studies have confirmed that IL-15 is sufficient in inducing differentiation of NK cells from early hematopoietic cells [34]. How IL-15 signaling in early haematopoietic cells results in NK cell differentiation is somewhat less clear, but many studies have contributed significantly to understanding the induction of NK cell development by IL-15. IL-15 expression in bone marrow stromal cells is upregulated by IRF-1 acting on an IRF response element in the IL-15 promoter (IRF-E) [35]. The induced IL-15 then acts on NK and NK T cell progenitors, stimulating their subsequent maturation [35, 36]. Therefore, upstream expression of the IRF-1 transcription factor is important for IL-15 expression and subsequent NK cell development. Additionally, transcription factors downstream of IL-15 signaling within the NK cell progenitor have also been identified. The transcription factor E4BP4 (also known as NFIL3) has been proposed as a NK cell lineage-specifying factor, since E4BP4-deficient mice show a severe reduction in NK cell numbers [37, 38]. E4BP4 was shown to be downstream of IL-15R signaling when addition of exogenous IL-15 was unable to rescue NK cell development in E4BP4-deficient progenitor cells [37]. Thus, transcription factors not only influence the expression of IL-15 (and probably its receptor), but also lie downstream of the IL-15R signaling pathway in NK cell progenitors to control subsequent stages of NK cell development.

Another way in which IL-15 signaling may affect NK cell development is through the induction of Ly49 receptors. Ly49 receptors mediate activating and inhibitory signaling in mature NK cells through interactions with MHC class I elements and are increasingly more appreciated as important mediators of “education” or “licensing” in developing NK cells [39, 40]. Some reports indicate that in NK cells lacking IL-15R α Ly49 expression is reduced [41]. Others have indicated that immature NK cells in IL-15 $^{-/-}$ mice do express Ly49 receptors, but these cells do not phenotypically develop beyond the “minor but discrete CD11b $^{-}$ CD27 $^{+}$ DX5 hi CD51 dull CD127 dull CD122 hi stage” [42]. Still others have used a model in which bone marrow (BM)-derived dendritic cells were prepared from mice transgenically modified to express varying amounts of IL-15 α to demonstrate that NK cell homeostasis, NK cell differentiation, and acquisition of Ly49 receptor and effector functions by NK cells require different levels of IL-15 trans-presentation input to achieve full status [43]. IL-15 promotes not only early NK cell development but is also suggested to be important for the differentiation of CD11b $^{+}$ CD27 $^{+}$ NK cells into CD11b $^{+}$ CD27 $^{-}$ fully matured NK cells, as monocytes need to express Tbet and IL-15R α for this maturation to occur [44]. Although many differences exist between mouse and human NK cell development, recombinant human interleukin-15 (rhIL-15) or an Adenovirus-vector expressing human IL-15 is able to significantly enhance NK cell development and maturation in the bone marrow and liver of Balb/c Rag2 $^{-/-}$ γ c $^{-/-}$ mice reconstituted with human hematopoietic stem cells [45]. Thus, varying levels of IL-15 stimulation in discrete microenvironments may induce different stages of NK cell development, and only further study will determine when, where, and how much IL-15 is available in vivo to the various stages in the NK cell lineage.

In addition to the requirement for IL-15 in optimal NK cell development and maturation, NK cells require IL-15 for their homeostasis in the periphery—that is to maintain normal numbers. Mature NK cells adoptively transferred into IL-15 $^{-/-}$ or IL-15R α $^{-/-}$ mice fail to proliferate, and their half-life of 7-8 days is reduced to only 2 days [46, 47]. The mechanisms by which IL-15 influences the homeostasis of NK cells are known to depend on IL-15's ability to induce Bcl-2 expression [46] and suppress both the forkhead box O3A (FOXO3A) and the pro-apoptotic factor Bcl-2-interacting mediator of cell death (BIM) transcription factors [48]. Interestingly, these vital signals are dependent on the transpresentation of IL-15 by IL-15R α -expressing dendritic cells [18]. Whereas mixed bone chimeras generated from IL-15R α $^{-/-}$ mice and IL-15R β $^{-/-}$ mice could support the survival of adoptively transferred NK cells, mixed bone chimeras generated from IL-15R α $^{-/-}$ and IL-15 $^{-/-}$ mice could not, indicating that IL-15 and its R α chain must be expressed by the same cells types to support the survival of NK cells [47, 49]. In complimentary experiments, forced expression of IL-15R on only dendritic cells (DCs) or treatment of mice with soluble IL-15 /IL-15R α complexes promotes the expansion of NK cell populations [50, 51]. In human NK cells, IL-15 sustains the expression of its high-affinity receptor, leading to long-lasting STAT5 phosphorylation and Bcl-2 expression important for the long-term survival of these cells [52].

Although survival of mature NK cells in the periphery is strictly dependent on transpresented IL-15, this requirement can be by-passed by transgenically forcing the constitutive expression of Bcl-2 [53]. However, even though numbers of circulating NK cells could be restored in these transgenic animals, the NK cells in these mice were impaired in their cytolytic activity [53]. More recent research suggests that IL-15 works additively with IL-10 to increase cytotoxicity of NK cells [54]. Glucocorticoids may also work synergistically with IL-15 to mediate activation of NK cells. Glucocorticoids when combined with IL-15 in cultures of peripheral blood (PB)-derived CD56 $^{+}$ cells induce increased cytolytic activity, IFN γ production, and expression of NKp30, NKp44, NKp46, 2B4, NKG2D and DNAM-1 [55]. These data imply that IL-15 is also an important signal in

the activation of NK cells. Dendritic cells (DCs) are known to activate NK cells [56], and IL-15 α expression by the DC is an essential component in its ability to activate NK cells, enhancing both cytolytic activity and IFN γ production [57]. Upon transient or prolonged exposure to IL-15 complexed to a soluble form of its receptor alpha chain *in vivo*, NK cells also undergo distinct phenotypic changes [58]. Importantly, transient stimulation augmented the NK cell pool and led to a more activated phenotype including increased CD69, NKG2D, and NKp46 expression; whereas chronic stimulation with IL-15 complexes appeared to impair NK cell activation and function [58]. Therefore, although future study is clearly warranted in this area, IL-15 may provide important signals for tuning the activation state of mature NK cells.

Mature NK cells are largely localized in the red pulp of the spleen and the sinusoidal regions of the liver; however, during viral infection they infiltrate the splenic white pulp and migrate rapidly to sites of infection [59]. The precise signals required for NK cell traffic in different situations are not well defined, but a small but convincing body of literature implicates IL-15 in the migration of NK cells from the circulation to sites of immunological insult. Only three years after the discovery of the cytokine, it was shown that NK cells would migrate to IL-15 in *in vitro* checkerboard chemotaxis assays and that these cells adhered more readily to a vascular endothelial cell line after stimulation with IL-15 [60]. Our own findings indicate that IL-15 is an important factor in recruiting NK cells from the circulation to the lung airways upon influenza infection, and NK cells from influenza-infected animals migrate to IL-15 in an *in vitro* transwell assay (Verbist, 2012, Publication Pending). Although IL-15 does appear to induce the migration of NK cells, it is unclear whether this is direct chemotaxis to the cytokine or an indirect effect due to modulation of other cell surface receptors. Stimulation with IL-15 is known to modulate CD11a expression on NK cells, thus increasing their adhesion to vascular endothelium [60]. Additionally, stimulation with IL-15 is known to alter the expression of several different chemokine receptors on the surface of NK cells. Expression of CX3CR1 is well described as a chemokine receptor whose expression is negatively regulated by IL-15 signaling through NFAT-dependent mechanisms [61, 62]. This effect appears to be specific to CX3CR1, however, as expression of CCR5 by NK cells is increased upon stimulation with IL-15, and expression of CXCR4 remains unaltered upon IL-15 stimulation [63]. In combination with glucocorticoids, treatment of PBMC-derived NK cells with IL-15 significantly increased surface expression of CXCR3 and CXCR4 [55].

Overall, IL-15 is a key regulator of NK cells, modulating all aspects of NK cell biology, including their development and maturation, survival and proliferation, activation and cytotoxicity, and migration to sites of inflammation. Thus, IL-15 is a vital part of NK cell responses, effecting a population of innate cells in sufficient number and capacity to respond to infection and limit viral replication.

2.2 IL-15 and Antigen-Presenting Cells

Although the immune system is frequently and conveniently broken down into innate and adaptive immunity, in reality there is no clear demarcation *in vivo* indicating the end of innate responses and the initiation of adaptive responses. Rather, a cascade of innate effectors is followed fluidly by a cascade of adaptive effectors whose functions are shaped by the signals of their predecessors. Although almost all cells of the innate immune system can affect those of the adaptive immune system, the key regulators of adaptive responses and long-considered “bridges” of innate and adaptive immunity are antigen presenting cells (APCs). APCs including dendritic cells and monocytes/macrophages are not only profoundly affected by IL-15 signals, but are also key producers of IL-15. Thus, IL-15 represents a cytokine signal that influences and informs both arms of the immune system and brings them together into a single, functional unit.

In response to infection, antigen-presenting cells must functionally mature to optimally prime cells of the adaptive immune system, and IL-15 plays an important role in this process. IL-15 stimulation enhances the phagocytic uptake of microbial pathogens by monocytes and macrophages and induces the production of pro-inflammatory factors such as IL-8 and monocyte chemoattractant protein 1 (MCP-1) by these cells [64]. IL-15 signaling in DCs may also lower the peptide concentration required for priming, as this has been shown to be the case in IL-15-stimulated DCs used to prime CTL responses to melanoma antigens [65], possibly because IL-15 stimulation increases levels of CD11c and MHC molecules, as well as CD40, CD80, and CD86 [66]. Similarly, IL-15 enhances IL-12 production and responsiveness, increases IFN γ production, and enables cross talk between conventional DCs and plasmacytoid DCs by upregulating CD40 on conventional DCs that allows interactions with CD40L-expressing plasmacytoid DCs [4, 67]. Furthermore, DCs from IL-15 deficient mice are impaired in their ability to prime delayed type hypersensitivity reactions or produce IL-2 and thus stimulate T cell proliferation [68, 69]. In contrast, in *in vivo* infection models, initial priming and proliferation of T cells in IL-15^{-/-} mice appears to be unaltered, with defects in T cell proliferation appearing only late in the memory phase [70, 71]. These differences may be accounted for by compensatory and/or redundant cytokine signals in active infections, that is, the context in which these cells are primed. Monocytes differentiated *in vitro* into DCs with GM-CSF and IL-15 initiate Th1 and Th17-type responses [72], and enhance NK cell production of IFN γ , leading to enhanced CD8 T cell induction [73]. There is little doubt, then, that IL-15 signaling in responsive APCs is an important part of shaping subsequent responses in specific lymphocyte populations.

Not only must antigen-presenting cells be able to receive signals from IL-15 to be fully functional, but in order to instruct the eventual functions of the cells they prime, antigen-presenting cells provide soluble IL-15 or transpresent it to the cells that they interact with. DCs matured with pathogenic stimuli such as poly I:C and LPS produce IL-15 in response [74]. The stimulation of DCs with covalently linked extracellular CD40L domains also induces the production of IL-15 and enhances T cell proliferation to *C. albicans* antigen [75]. In anti-viral immune responses, type 1 interferons serve as a potent inducer of IL-15 expression, since the IL-15 promoter contains an interferon regulated element [74, 76]. Once APCs are induced to express IL-15, NK and T cells are able to respond to these signals, continuing the evolution of the immune response to the invading pathogen. It has been shown, for example, that monocytes activate NK and NKT cell proliferation and LMP1 expression through transpresented IL-15 [77]. Additionally, DC-derived IL-15 is required for tumoricidal NK activity [78] as well as CD69 expression, IFN γ secretion, and proliferation [79]. IL-15 presented by dendritic cells to anti-viral CD8 T cells is also important for the generation and maintenance of these responses in both systemic viral infections [80] and at specific sites following tissue-specific infections [81], partially because IL-15 expression by DCs in response to signals from Ag-specific CD4 cells is an important mechanism by which CD8 T cells escape TRAIL-mediated apoptosis during immune reactions [82].

2.3 IL-15 and CD8 T Cells

CD8 T cells express all three components of the IL-15 heterotrimeric receptor. Although T cells constitutively express very low levels of IL-15R α [6], expression of this receptor chain is induced by stimulation with IL-2, anti-CD3 antibody, or phorbol-myristate acetate. CD122 is constitutively expressed by T cells; although, CD8 T cells express much higher levels of this receptor chain than CD4 cells, and memory subsets express higher levels than naïve subsets [83]. In general, IL-15 signals are thought to be more important for the homeostasis of memory CD8 T cells than other T cell subsets. Signaling through the IL-15 receptor is known to be coupled to Jak1 and Jak3 activation and phosphorylation and

nuclear translocation of STAT3 and STAT5 [84, 85]. Additionally, IL-15 signaling in T cells results in the phosphorylation p56lck and p72syk, induction of the MAP kinase pathway, and induction of Bcl-2 [4, 86]. These signals are important for the survival of T cell populations, especially memory populations whose survival is dependent on cytokine stimulation and independent of antigen.

Paralleling NK cells, IL-15 signaling affects all phases of CD8 T cell biology, including their development, activation, proliferation, survival, and cytotoxicity (Figure 2). NK cells, however, appear to have much stricter requirements for IL-15 for their development than CD8 T cells. Original analyses of IL-15^{-/-} and IL-15Rα^{-/-} mice revealed reductions numbers of CD8 T cells that could be found in the periphery, but these deficiencies were largely restricted to the memory (CD44^{hi}) population [31, 32]. These data would suggest that the early development of naïve TCRαβ CD8 T cells is minimally dependent on IL-15. Indeed, these findings are consistent with earlier studies that suggested that IL-15 is expressed only by thymic stromal epithelial cells and only at very low levels, which is important for promoting the development of TCRαβ T cells from thymic bipotential T/NK progenitor cells, as high concentrations of IL-15 promoted the development of TCRγδ CD8 T cells and NK cells instead [87]. Nonetheless, thymic IL-15 may subtly affect naïve CD8 T cell development. Although IL-7 is well-known to be critical in normal thymocyte development, γc^{-/-} mice have a more severe thymocyte defect than IL-7Rα^{-/-} mice [88, 89]. Furthermore, IL-7Rα^{-/-} IL-2Rβ^{-/-} double mutant mice display a similar thymic phenotype to γc^{-/-} mice, while IL-7Rα^{-/-} IL-2^{-/-} double mutant mice phenotypically resemble IL-7Rα^{-/-} mice [90]. These observations suggest that IL-7Rα independent signals that utilize IL-2Rβ and γ chains independently of IL-2 (likely IL-15) are important in fine-tuning thymocyte development [30].

Once CD8 T cells have made their exodus from the thymus, IL-15 provides CD8 T cells in the periphery proliferative signals in steady-state conditions. This has been evidenced by the fact that lymphocytes from un-immunized IL-15Rα^{-/-} mice proliferate at a lower rate *in vivo* compared with lymphocytes from normal mice [31]. In reverse experiments, injection of IL-15 causes the selective proliferation of memory phenotype CD8⁺ T cells [76]. Consistent with these findings, IL-15 transgenic mice that over-express IL-15 have increased numbers of memory phenotype CD8 T cells [91, 92], and delivery of IL-15 complexed to its Rα chain induces the robust proliferation of memory phenotype CD8 T cells and (to a lesser extent) naïve CD8 T cells [51]. There is evidence, however, that even this naïve CD8 T cell response to IL-15 complex depends on interactions with MHC I and the avidity of the TCR [93]. Thus, in the absence of an antigenic stimulus, IL-15 delivers a proliferative signal to CD8 T cells; however, it remains unclear how important this signal is to naïve CD8 T cells in the periphery, as all of these studies together implicate a more important role for IL-15 in the proliferation of memory (or at least memory phenotype) CD8 T cells.

While IL-15 may support the basal proliferation of naïve CD8 T cells to some degree, it may be important for their proliferation in lymphopenic environments. When T cells are transferred into lymphopenic conditions, IL-15 is a potent inducer of homeostatic proliferation. In experimental models of homeostatic proliferation, small numbers of T cells (e.g. (1–2) × 10⁶ cells per mouse) are transferred into either constitutively (e.g. RAG-1^{-/-} or RAG-2^{-/-} mice), or transiently (e.g. sublethally irradiated or anti-TCR mAb treated) lymphopenic mice. Transfer of naïve T cells into sublethally irradiated IL-15^{-/-} hosts leads to reduced proliferation compared with normal hosts (although this deficit is not as profound as in IL-7^{-/-} hosts) [94–96]. The increased expression of IL-2Rβ on naïve T cells undergoing homeostatic proliferation suggests that signals delivered through IL-2R β containing receptors may involved in this process, and IL-15 appears to be an important

signal not for initiating homeostatic proliferation, but rather for its continuation [97]. Interestingly, naïve CD8 T cells homeostatically proliferating or proliferating in response to IL-15 complexes acquire a memory-like phenotype, expressing CD44, Ly6c, and CD69 [51, 98]. Thus, IL-15 contributes to the sustained homeostatic proliferation and possibly the phenotypic conversion of naive cells during this process.

In addition to providing the stimulus for CD8 T cells to proliferate, IL-15 has been shown to be an important survival factor for these cells. IL-15 can protect lymphocytes from undergoing programmed cell death; although, this function may not be independent of its ability to promote proliferation, as IL-15 appears partially influence cell survival by causing them to enter the cell cycle [30]. *In vitro*, the induction of anti-Fas-mediated apoptosis can be prevented in cultures of concanavalin A-treated human T lymphocytes by the addition of IL-15 to these cultures [99]. Co-culture with IL-15 also rescued *ex-vivo* T cells from AD10 transgenic mice that were induced to undergo apoptosis by previous injection of with the Vβ3 family inducing superantigen SEA [100]. A role for IL-15 in preventing cell death has also been demonstrated *in vivo* by protection of mice injected with an anti-Fas antibody with administration of a chimeric human IL-15-murine IgG2b fusion protein [99]. Thus, IL-15 is able to protect T cells against apoptotic cell death. All the mechanisms by which IL-15 protects cells from undergoing programmed cell death in different circumstances have not been fully delineated, but IL-15 is known to upregulate expression of anti-apoptotic proteins (most notably Bcl-2) and cause entry into the cell cycle.

Initial activation of CD8 T cells is a consequence of engagement of specific TCR and peptide-loaded MHC I molecules on APCs and non-specific engagement of costimulatory molecules. These events proceed independently of any cytokine signaling; however, these events bring T cells into close and prolonged interactions with APCs during which APCs can provide multiple cytokine stimuli, an important one of which is transpresented IL-15. Expression of both IL-15Rα and CD122 increases after TCR activation, and heterologous IL-15 can support the survival and/or proliferation of activated T cells [100]. Similarly, addition of IL-15 to mice augmented specific T cell proliferation and cytotoxicity to SIINFEKL-pulsed DCs [101]. Contact with IL-15 and especially signaling through CD122 seem to be essential factors in differentiating activated CD8 T cells. Whereas strong, prolonged signaling through CD122—effected by IL-2 binding—promotes terminal effector differentiation, weaker and intermediate-strength signaling through CD122—effected by IL-15 binding—promotes central memory development and survival [102]. This is consistent with evidence that IL-2, but not IL-15, is essential for the generation of primary effector responses [103] and the dispensability of IL-15 in primary CD8 T cell responses to various pathogens (discussed below). Although these cells are generated in the absence of IL-15 signaling, the prolonged survival of effector CTLs through the contraction phase is highly dependent on IL-15 [104, 105], and this is especially true of CD127^{lo}, KLRG-1^{hi} short-lived effector cells [105, 106]. The long-term maintenance of established memory pools of CD8 T cells is thought to be highly dependent on IL-15 transpresentation, but recent evidence suggests that primary human CD8 T cells do not require transpresentation of human IL-15 *in vitro* [107]. While human CD8 T cell proliferation can be boosted by IL-15 transpresentation [108], cis-presentation (IL-15 bound to IL-15Rα is presented to CD122/γc heterodimers on the same cell surface) occurs more efficiently in the human receptor-ligand combination than in that of the mouse system [107]. These results imply that the maintenance of memory CD8 T cells may be achieved via distinct mechanisms in humans and mice, though both systems utilize IL-15 signaling to achieve lasting populations of memory CD8 T cells.

As early as 1995—only a year after its discovery—a role for IL-15 in the chemoattraction of T cells was described [109]. IL-15-induced migration of T cells is likely very important for

the arrival of effector CTLs at sites of inflammation and/or infection. In models of rheumatoid arthritis, for example, IL-15 is abundant in synovial fluid and can the migration of human PBMCs in vitro [110]. In responses to influenza infection, IL-15 has been shown to induce the migration of effector CD8 T cells to the lung airways [111]. Similar to the IL-15-induced migration of NK cells, it is unclear whether chemoattraction of T cells by IL-15 is a result of direct chemotaxis, indirect modulation of molecules important for lymphocyte migration, or some combination of the two. IL-15 has been shown to induce the expression of both chemokines and their receptors in T cells, and IL-15 promotes T cell extravasation through endothelial cells via a CD44-dependent mechanism [112]. The expression of the adhesion molecules CD44, LFA-1, and CD62-L are aberrantly expressed on CD8 T cells from IL-15R α ^{-/-} mice, and splenocytes from IL-15R α ^{-/-} mice were less efficient than normal splenocytes at entering peripheral lymphoid organs after intravenous injection [31].

Therefore, in parallel to the many ways in which IL-15 regulates NK cell biology, IL-15 represents an integral part of shaping anti-viral CD8 T cell responses. IL-15 promotes the survival and proliferation of CD8 T cells at all stages of the immune responses (especially the memory phase), enhances the cytotoxicity of effector CD8 T cells, and signals T cells either directly or indirectly to enter infected locales.

3. IL-15 and Anti-Viral Immunity

3.1 Systemic Viral Infections

The effects of IL-15 on the outcome of virally-mediated diseases vary greatly from virus to virus. Because IL-15 is a potent activator of NK and CD8 T cell populations, viral diseases whose control largely depends on NK and CD8 T cell may be aggravated by an IL-15 deficiency whereas viruses that cause lympho-proliferative disorders may be ameliorated by the loss of IL-15. One such example of the latter is human T cell lymphotropic virus type 1 (HTLV-1). HTLV-1 causes a neurological disease termed HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) with clinical manifestations similar to those of multiple sclerosis. The increased proliferation of lymphocytes in HAM/TSP-infected individuals can be partially attributed to increased expression of IL-15R α and increased production of the cytokine itself, and blocking antibodies against IL-15 or its receptor blocks some proliferation [113, 114]. In addition to increasing their proliferation, IL-15 signaling may also increase the activation status of lymphocytes in these patients by enhancing their effector capabilities, causing spontaneous degranulation and IFN γ secretion [115]. Thus, in diseases such as HAM/TSP, wherein viral infection results in expansion of the lymphocyte pool, blocking IL-15 signaling may be an important therapeutic option. In fact, the humanized antibody Mik β 1, a blocking antibody against CD122 is in clinical trials for HAM/TSP patients (<http://clinicaltrials.gov>).

In viral infections, far more common than the desire to reduce lymphocyte proliferation and activation is the desire to augment lymphocyte numbers and cytotoxicity to such a degree that they are potent effectors able to control and eliminate the viral pathogens. The potential role for IL-15 in this process has been investigated in a variety of models of viral pathogens. An absence of IL-15 poses no problems in the acute phase of infection with either vesicular stomatitis virus or lymphocytic choriomeningitis virus, as IL-15^{-/-} mice clear these viruses [70, 71, 80]. In contrast to the unaltered control of viral load in IL-15^{-/-} mice infected with VSV or LCMV, infection of IL-15^{-/-} mice with vaccinia virus results in a loss of control of viral replication, and these animals succumb to infection [32]. These differences likely reflect differential roles for NK cells in immune responses to these viruses. NK cells are thought to help control the initial replication of vaccinia virus, but robust NK cell responses to LCMV play little role in viral clearance and may actually be immunoregulatory,

suppressing T cell responses that are critical in controlling this infection [116]. Regardless of whether or not IL-15 is necessary for NK cell responses and/or viral clearance, IL-15 is not unimportant in immune responses to VSV and LCMV infections. Models of intravenous infection of mice with these viruses have revealed that IL-15 is important for the generation of antigen-specific memory CD8 T cells responding to VSV infection [80]. While a similar requirement for IL-15 in the generation of memory CD8 T cells was not observed following LCMV infection, in both viral infection models, IL-15 is requisite for the long-term maintenance of the antigen-specific memory CD8 T cells, as this population wanes dramatically over time following infection [70, 71, 80].

3.2 Tissue-Specific Viral Infections

In contrast to the gradual attrition of antigen-specific memory CD8 T cells in IL-15^{-/-} mice infected with VSV or LCMV, IL-15^{-/-} mice infected with either latent gammaherpesvirus (MHV-68) or influenza virus show no defects in the antigen-specific memory CD8 T cells [117, 118], even though the decline of these cells from specific sites (namely, the lung airways) has been associated with loss of IL-7 and IL-15 receptors [119]. This difference may be partially accounted for by the continual presence of antigen from reactivation of the gammaherpes virus [117], but viral persistence is likely not the main factor maintaining memory CD8 T cells in the absence of IL-15 following a low dose influenza infection, since IL-15^{-/-} mice clear this virus with kinetics similar to wild type mice in primary and challenge infections ([118] and unpublished observations). IL-15-independent memory CD8 T cells in this model, then, may be a result of the mucosal environment in which these CD8 T cells are primed, since there is also no attrition of CD8 memory T cells following an intranasal infection with vesicular stomatitis virus [118]. Thus, immune responses primed in specific tissues may impart transcriptional programs on responding CD8 T cells that renders these cells more or less dependent on IL-15 for their homeostasis.

IL-15 is not required for positive disease outcome or maintenance of a memory CD8 T cell population in the aforementioned tissue-specific viral infections, but IL-15 is not unimportant in tissue-specific viral infections. It has been repeatedly observed that viruses induce expression of IL-15, and this expression is important for anti-viral responses by different lymphocyte populations. Infection with hepatitis B, for example, induces IL-15 expression, and low levels of circulating IL-15 are associated with high viremia and poor disease outcome [120]. In individuals infected with hepatitis C, there is no correlation between the disease and IL-15 expression, but *in vitro* studies have shown that IL-15 treatment promotes the proliferation and survival of NK cells, a cell population that is known to be important in the control of hepatitis C replication in the liver [121]. Thus, in both diseases, suboptimal production of IL-15 is correlated with the likelihood of the virus entering a chronic phase, presumably because protective NK cell responses cannot be maintained in absence of IL-15. IL-15 production is also known to be upregulated in response to respiratory viruses such as RSV [122] and influenza [111]. In the latter, local IL-15 production appears to be important for the optimal recruitment of NK and effector CD8 T cells to the site of infection and their prolonged survival in the lung airways [81, 111].

Following infection with herpes simplex virus-2 (HSV-2), IL-15^{-/-} mice are unable to control the pathogen and the infection is lethal—effects thought to be mainly mediated by the lack of NK and NKT cells in these animals [123]. *In vitro* evidence corroborates these conclusions, as IL-15 has been shown to have antiviral effects on isolated human PBMCs infected with HSV-1, Epstein barr virus, or herpes virus-6, mainly through its action on NK cells [124], but additional studies with HSV-2 report a critical role for IL-15 in the innate immune response for protection independent of any action on natural killer cells [125]. These studies were further corroborated by more recent studies in which IL-15^{-/-} mice were

not protected against HSV-2, but wild type animals depleted of natural killer cells were [126]. Although it is somewhat unclear as to the mechanism by which IL-15 mediates protection in this herpes model, it is known that effective CD4 responses are essential for viral clearance, and IL-15 supports the basal proliferation of CD4 cells and enhances the TCR-dependent proliferation of Th1/Th17 (IFN γ , IL-17 double positive) cells [127]. However, over-expression of IL-15 during HSV-2 infection compromised CD4-mediated protection, presumably by expanding the CD8 T cell compartment to such an extent that it out-competed the CD4 compartment for limited resources [128]. On the whole, how IL-15 signaling affects the cell population most important for control of a pathogen determines the importance of IL-15 as an immune modulator in that system. Thus, it is of critical importance that the role of IL-15 be examined in individual infections: systemic or mucosal.

3.3 Chronic Viral Infection/HIV

The chronic virus-mediated disease in which immune intervention via IL-15 targeting has received the most attention is Human Immunodeficiency Virus (HIV). IL-15 treatment has been explored as a method of enhancing NK cell responses to control viral replication, immune restoration in patients in whom antiretroviral therapy is sufficient to suppress viral load but T cell counts remain low, and as a potential for vaccines designed to elicit robust T cell memory [129]. Non-human primate models are most widely used to investigate the immunological benefits of candidate therapies in immunodeficient settings. In SIV models, IL-15 has been shown to increase effector functions of specific CD8 T cells. In vitro, IFN γ production by CD8 T cells from SIV and SHIV-infected macaques was increased by IL-15 stimulation [130]. When administered as a treatment in vivo to chronically SIV infected macaques, IL-15 augmented populations of effector memory CD8 T cells [131]. IL-15 treatment has also been shown to augment populations of effector memory CD4 T cells in anti-retroviral treated animals [132]. Although IL-15 treatment had no effect on viral load in either of these studies, the ability to expand effector memory CD8 and CD4 T cell compartments reveal potential for this mode of treatment in immune reconstitution. In similar studies, a reduction in viral load was reported in animals co-immunized with IL-15 expression plasmids, but differences in viral titers were only discernible after the release of anti-retroviral treatment [133]. Additionally, IL-15 treatment alone or in combination with IL-2 was effective at inducing new CD4 and CD8 memory to influenza and tetanus toxins, indicating that IL-15 treatment may also be effective in ameliorating the severe consequences of coinfection in HIV-infected individuals [134]. In studies of human immunodeficiency virus (type 1), in vitro studies have revealed that IL-15 can increase IFN γ production and chemokine secretion by NK cells isolated from HIV-1-infected subjects [135]. Increased IFN γ production, enhanced cytotoxicity, and protection from apoptosis upon IL-15 treatment in vitro has also been shown for CD8 T cells isolated from HIV-1-infected subjects [136].

Although several studies suggest that IL-15 shows substantial promise as a therapeutic for HIV infections, evidence also exists that IL-15 may exacerbate disease. Because IL-15 treatment expands T cell populations, the treatment could increase viral targets and lead to increased viral load [129]. In models of acute SIV infection, IL-15 treatment increased viral setpoint by 3 logs and accelerated disease progression in 2 out of 6 animals [137], and as a vaccine adjuvant had no benefits [138]. In follow up studies attempting to address the mechanism by which IL-15 exacerbated disease, it was found that CD4 T cells cultured with IL-15 and/or SIV increased their density of CD4 expression, leading to higher infection levels [137]. These studies were supported by additional studies correlating high viremia during the acute phase of infection with high levels of IL-15 in plasma [139]. In models of chronic SIV infection, however, IL-15 treatment resulted in no difference in viral load when compared with the control group [140]. With regards to HIV-1, in vitro studies using

isolated PBMCs stimulated with PHA indicated that IL-15 stimulation enhanced viral replication [141]. These observations that IL-15 could increase viral replication lead to the hypothesis that IL-15 might be an effective vaccine adjuvant, increasing the immunogenicity of the vaccination. Indeed, HIV DNA vaccines co-infected with the IL-15 gene enhanced CD8 T cell responses [142], and similar platforms in which DNA vaccines encoding SIV antigen were coinjected with an IL-15 containing plasmid were associated with enhanced protection from an SHIV (SHIV 89.6P) challenge when compared to animals receiving the vaccination alone [143]. Comparable studies, however, report no clinical differences between vaccinated and vaccinated plus IL-15-adjuvanted groups in terms of viral load, although adjuvanted animals did exhibit increases in SIVgag-specific T cell responses [144]. Finally, when IL-15 was employed to adjuvant a vaccine to a more virulent challenge virus, SIV mac251, the IL-15-induced proliferation of viral targets appeared to abrogate any benefits from the vaccine itself [145]. Therefore, while IL-15 seems to have little potential as an HIV vaccine adjuvant, the consistently reported expansion of effector memory T cell populations without disease exacerbation in the chronic phase suggests that IL-15 may be an effective therapeutic for immune reconstitution in HIV-infected individuals.

3.4 IL-15 and Immune Intervention to Viral Pathogens

Because IL-15 production in response to viral infection appears to be an important mechanism of immune control, there has been considerable interest in trying to use IL-15 expression as a method of adjuvanting vaccines and/or improving immune responses to viral pathogens. These interests have been further encouraged by the development of IL-15-expression vectors and therapeutics for immune-intervention and reconstitution for HIV, and their application has been gradually expanded to include various other viral pathogens (Table 1). Indeed, such strategies have met some successes. A vaccinia-virus-based vaccine platform was engineered to express the hemagglutinin and neuraminidase from H5N1 influenza viruses as well as IL-15. This vaccine induced cross-neutralizing antibody responses and robust cellular immune responses that conferred cross-clade protection to mice challenged with different H5N1 viruses [146]. Intranasal delivery of recombinant IL-15 complexed to its α chain has also been therapeutically exploited following influenza infection. Introduction of IL-15 complexes to the lung airways of influenza-infected mice lead to enhanced lymphocyte migration to the site of infection and improved control of viral replication early and during challenge infections ([111] and unpublished observations). Additionally, a smallpox vaccine with integrated IL-15 has been shown to protect cynomolgus monkeys from a lethal dose of monkeypox virus administered three years post vaccination [147]. Enhanced immune responses to plasmid DNA vaccination by IL-15 was also reported against hepatitis B surface antigen [148] and the HSV-1 glycoprotein B [149]. However, not all attempts have yielded such promising results. Immunizing rhesus macaques with different doses of IL-15 expressing plasmid in an influenza immunogenicity model, Yin et al. found that whereas low doses of IL-15 were effective at improving T cell responses, high doses of IL-15 (4mg) decreased production of IFN γ and T cell proliferation [150]. These data highlight the importance of optimizing adjuvants but overall reveal a significant potential for IL-15 as an effective strategy for improving vaccines to viruses.

4. Conclusions

The wide range of functions from IL-15 signaling in so many different cell types makes IL-15 an attractive target for immune intervention, but also demands caution in doing so. The many shared receptor components results in functional redundancy with other cytokines, and the broad tissue distribution of IL-15R α , the potential to activate multiple signaling pathways, and the layered regulation of cytokine expression all dictate that the context in which a cell encounters IL-15 will be critical in determining the functional output

of that cell type. An important consideration is that IL-15 is known to signal through several receptor permutations. Classically, and importantly for its role in maintaining NK and T cell populations, IL-15 is transpresented to responsive cells expressing CD122 and CD132 by cells expressing the cytokine itself and R [10, 30, 151]. It has also been demonstrated, though, that soluble IL-15 is able to signal through the high affinity heterotrimeric receptor complex [152], an intermediate affinity dimeric receptor consisting of CD132 and R [153], and through the receptor alpha chain alone [4, 154, 155]. Although these numerous potential signaling pathways of IL-15 complicate the ability to develop IL-15 as an effective immune therapy, they also help explain how IL-15 mediates so many diverse functions and provides opportunities for more focused or targeted immune therapies.

Abbreviations

IL-15	(interleukin-15)
γc	(common gamma chain)
NK	(natural killer)
Teff	(effector T cells)
Tmem	(memory T cells)

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1. .
Figure 1

2. .
Figure 2

Table 1

Strategies of IL-15 therapies in virus-mediated diseases.

Disease	Treatment	Effects	Model	Ref.
HAM/TSP	Humanized MİKβ1 (anti CD122)	Reduced Lymphocyte Proliferation and Activation	Human Clinical Trials	Humanclinicaltrials.gov
SHIV (SHIV89.6P)	SHIV Plasmid DNA + IL-15 Expression Plasmid	More Rapid Control of Challenge Infection	Rhesus Macaques	[139]
SHIV (SHIV89.6P)	SHIV Plasmid DNA + IL-15 Expression Plasmid	No Effect	Rhesus Macaques	[140]
SIV (SIVmac251)	SIV Plasmid DNA + IL-15 Expression Plasmid	Abrogation of Vaccine Benefits with Cytokine Adjuvant	Rhesus Macaques	[141]
SIV (SIVmac251)	SIV Plasmid DNA + IL-15 Expression Plasmid and a Replicating Adenovirus-SIV with SIV Protein Boosting	No Control of Vaginal Challenge	Rhesus Macaques	[134]
Chronic SIV (SIVmac251)	1°: SIV Plasmid DNA + ART Boost: SIV Plasmid DNA + IL-15/IL-15Rα Expression Plasmid	Increased T Cell Responses and Decreased Viral Load After Release of ART Treatment	Rhesus Macaques	[129]
Influenza	Vaccina Virus Expressing Influenza Coat Proteins and IL-15	Increased Cellular and Humoral Responses and Cross-Clade Protection Against a Variety of H5N1 Challenge Infections	Mice (BALB/c)	[142]
Influenza	H3N2 Immunization + Intranasal IL-15/IL-15Rα Complexes	Increased Specific T Cell Responses and Enhanced Clearance of H1N1 Challenge	Mice (C57Bl/6)	[114]
Monkeypox	Smallpox Vaccine (Wyeth Vaccinia) with Integrated IL-15	Milder Symptoms and Enhanced Recovery to Challenge with Lethal Monkeypox (Zaire 79 MA-104)	Cynomolgus Monkeys	[143]
Hepatitis B	Hep B Plasmid DNA + IL-15 Expression Plasmid	Enhanced Specific T Cell Responses	Mice (BALB/cJ)	[144]
HSV-1	HSV-1 Plasmid DNA + IL-15 Expression Plasmid	Elevated Survival Rates After Lethal HSV-1 Challenge	Mice (BALB/c)	[145]
Influenza	Influenza Plasmid DNA + Low or High Dose IL-15 Expression Plasmid	Low Dose IL-15: Increased T Cell Responses High Dose IL-15: Decreased T Cell Responses *No Differences in Hemagglutinin Inhibition Antibody Titers	Rhesus Macaques	[146]