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Review Article

# 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 (γc) cytokine signals for their development and homeostasis. The γc 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.



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

IL-15 is a γc 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 γc, and CD122 (IL-2 Rβ) [2,7]. Specificity for a cytokine is conferred to each receptor by a private α chain, CD25 or IL-15Rα 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

*Abbreviations:* IL-15, interleukin-15; γc, common gamma chain; NK, natural killer; Teff, effector T cells; Tmem, memory T cells.

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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 mediating antiviral responses through cytokine release (such as IFN $\gamma$) 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 $\gamma$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 (NK) 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$\alpha^{-/-}$ 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$\alpha$ [33]. The necessary expression of CD122 and IL-15R$\alpha$ 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$\alpha$ 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$\alpha$ 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$\alpha$ 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$^{-/-}\gamma$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