

The Pleiotropic Functions of Interleukin 15: Not So Interleukin 2–like After All

By Averil Ma, David L. Boone, and James P. Lodolce

From the Department of Medicine and the Committee on Immunology, University of Chicago, Chicago, Illinois 60637

Since its discovery in 1994, IL-15 has been studied in the context of its structural cousin, IL-2 (1). Early biochemical and *in vitro* lymphocyte studies revealed many similarities between IL-15 and IL-2: (a) IL-2 and IL-15 constitute the only two members of a family of cytokines containing a four α helix bundle; (b) the heterotrimeric receptors for IL-2 and IL-15 share both the IL-2/15R β and IL-2R common γ (IL-2R γ or γ_c) chains; (c) the shared IL-2/15R β and γ_c chains are responsible for downstream cytoplasmic signals; and (d) the IL-2R α and IL-15R α chains, which confer specificity to IL-2R and IL-15R for their respective ligands, are closely related proteins (2). However, the highly restricted expression of IL-2 and IL-2R α to activated T cells suggests that IL-2R signals perform unique functions in adaptive T cells, whereas the pleiotropic expression of IL-15 and IL-15R α hints at a much broader role for IL-15R in multiple cell types. Indeed, distinct functions for IL-2 and IL-15 have been suggested from *in vivo* studies. IFN regulatory factor (IRF-1)-deficient mice lack NK cells due to an inability of their bone marrow stroma to elaborate IL-15, demonstrating a unique role for IL-15 in supporting NK cell development (3). Comparative studies of IL-2R α -deficient and IL-2/15R β -deficient mice (where only the latter should lack IL-15R signals) suggest that IL-15 might also be important for the differentiation of NK T cells and certain subsets of intraepithelial lymphocytes (IELs) (4, 5). Finally, exogenous IL-15, but not IL-2, selectively induces the proliferation of memory phenotype CD8⁺ T cells in normal mice (6). Thus, emerging from the shadow of IL-2, IL-15 may serve a wide range of immune functions.

The unique roles for IL-15 *in vivo* have become clearer with the initial reports of IL-15-deficient (IL-15^{-/-}) mice by Kennedy et al. in this issue (7) and IL-15R α -deficient (IL-15R α -/-) mice (8). While IL-2^{-/-} and IL-2R α -/- mice spontaneously accumulate activated T and B cells and die prematurely from autoimmune disease, IL-15^{-/-} and IL-15R α -/- mice are

generally healthy, lymphopenic, and specifically lack NK cells, NK T cells, intestinally derived subsets of IELs, and activated CD8⁺ T cells (7–10). The loss of these cells demonstrates that IL-15 signals via IL-15R α are critical for lymphoid development and/or maintenance, particularly for innate immune cells. By showing that 7 d of IL-15 treatment salvages these cells, Kennedy et al. suggest that the peripheral maintenance of these cells may be a prominent aspect of IL-15 function (7). This observation is consistent with prior work indicating that IL-15 supports peripheral memory phenotype CD8⁺ T cells (6, 8). It also suggests that CD8⁺ T cells may partially resemble innate immune cells. Furthermore, IL-15 also induces the activation and cytotoxicity of mature NK cells (11). In addition, IL-15 clearly regulates innate immune cell differentiation. Bone marrow stroma elaborates IL-15 to support NK cell differentiation (3, 12), and IL-15 skews the differentiation of thymic progenitors towards NK T cells (13; Fig. 1). Thus, IL-15 is critical for mediating the development, homeostasis, and activation of innate immune cells.

The finding that IL-15^{-/-} and IL-15R α -/- mice are lymphopenic suggests that IL-15 may also support adaptive CD4⁺ and CD8⁺ T cells (7, 8). Whether IL-15 regulates adaptive lymphocyte differentiation remains to be elucidated, but the reduced thymic cellularity of IL-15R α -/- mice suggests that this may be the case (8). Nevertheless, it is clear that IL-15 provides tonic proliferative and/or survival signals to support mature lymphocytes (6–8). As IL-15 is elaborated by nonlymphoid (stromal and epithelial) cells, physiological delivery of IL-15 to adaptive T lymphocytes may predominantly occur within nonlymphoid stroma. For example, both muscle and epithelial cells express and respond to IL-15, so tissue-bound lymphocytes may share these tissue pools of IL-15 and use them for homeostatic maintenance (14, 15). In this context, the intestinal mucosa—which harbors large numbers of innate immune cells responding to luminal microbes, and whose epithelial and stromal cells elaborate IL-15—is an excellent microenvironment for such interactions. Future studies of mucosal and other tissue-bound lymphocytes are thus likely to reveal novel insights into how IL-15 supports lymphocyte homeostasis.

Address correspondence to Averil Ma, University of Chicago, 5841 S. Maryland Ave., MC6084, Chicago, IL 60637. Phone: 773-834-0687; Fax: 773-702-2281; E-mail: ama@medicine.bsd.uchicago.edu

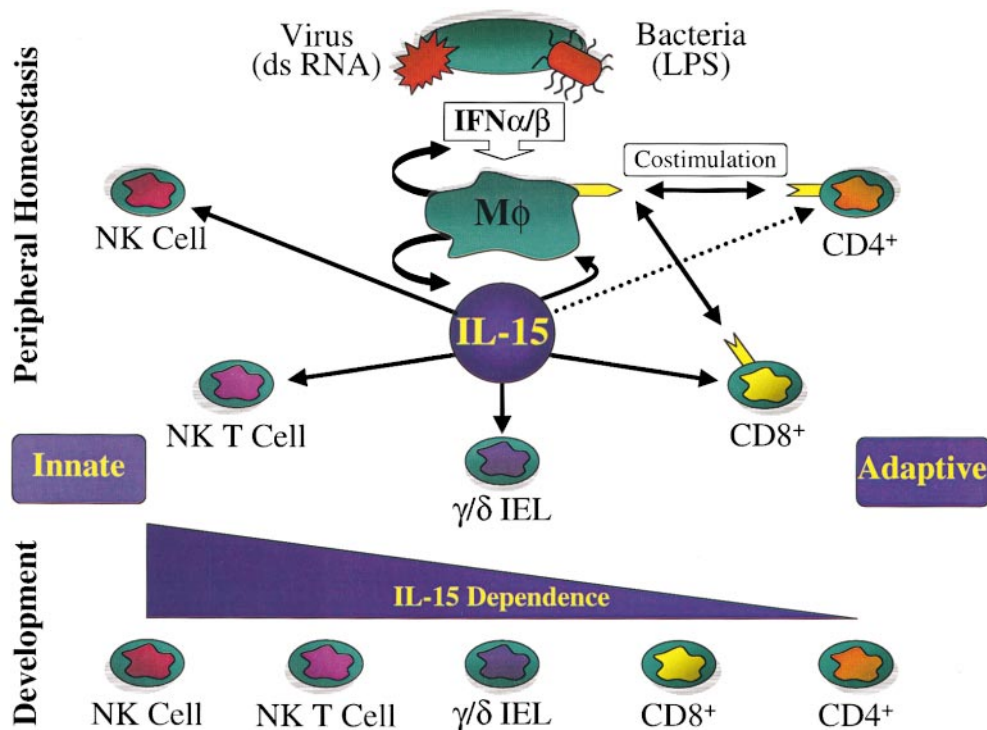


Figure 1. IL-15 preferentially supports innate immune cell development and homeostasis. Upon bacterial or viral infection, conserved motifs (such as double-stranded [ds] RNA or LPS) result in the release of type I IFNs (IFN- α/β) from infected host cells. Type I IFNs activate macrophages (M ϕ), stimulating them to produce IL-15 as well as inducing the upregulation of co-stimulatory molecules. IL-15 selectively activates NK cells, NK T cells, intestinal γ/δ T cells (γ/δ IEL), and CD8 $^+$ T cells. From a developmental standpoint, innate immune cells also appear to rely more on IL-15R signals.

The propensity of antigen-experienced, or memory, T lymphocytes to circulate through nonlymphoid tissues suggests that IL-15 function may extend to the maintenance of immunological memory. Because memory T cells may express elevated levels of IL-15R α and IL-2/15R β as a result of antigenic exposure, they may proliferate and survive in response to tissue-derived IL-15. As noted above, such stimulation could occur within nonlymphoid stroma, in the relative absence of cognate antigens, active inflammation, or lymphocyte-derived cytokines. Moreover, IL-15 is expressed by activated endothelial cells and may regulate the capacity of T lymphocytes to migrate across endothelial barriers to target tissues (16). Thus, several approaches may be required to fully understand the scope of IL-15's potential memory function. It will also be important to determine which cellular sources of IL-15 are responsible for supporting memory cells. How IL-15 may be involved in the maintenance of immunological memory is clearly an important and testable issue that is greatly facilitated by the availability of IL-15 $^{-/-}$ and IL-15R $\alpha^{-/-}$ mice.

An essential role for IL-15 in immune responses is highlighted by the inability of IL-15 $^{-/-}$ mice to survive vaccinia virus infection (7). While NK cell antiviral responses are likely to be compromised in these mice, the selective loss of memory phenotype CD8 $^+$ T cells also raises the possibility that CD8 $^+$ T cell antiviral responses may also be defective. Since CD8 $^+$ T cells resemble classical innate immune cells in their homeostatic reliance on IL-15, and since IL-15 activates NK cells, it is possible that IL-15 also stimulates CD8 $^+$ T cell cytolytic competence. Additional studies are now needed to define which IL-15 function(s) is essential for successful antiviral responses. Other immune

responses may be less reliant on IL-15, and understanding the role(s) of IL-15 in different systems should lead to a better understanding of the mechanisms by which different immunogens induce distinct innate (and subsequently, adaptive) immune responses (17; Fig. 1). Moreover, manipulating the expression or activity of IL-15 and IL-15R α (perhaps in conjunction with other costimulatory molecules) will likely be an important area for modulating immune responses.

The fate of activated T lymphocytes to undergo programmed cell death or persist as memory cells is central to the regulation of immune responses. In this context, it is essential to note that activated cells express both IL-2R α and IL-15R α . IL-2 predisposes activated T cells to undergo programmed cell death, whereas IL-15 appears to support proliferation (and possibly survival), so these cells must distinguish between IL-2R and IL-15R signals. The importance of this distinction is emphasized by the divergent phenotypes of the mutant mice. This difference forces us to return to the IL-2R and IL-15R signaling complexes and ask how the distinction is made. Ligand availability is likely to be a major factor; activated T cells are the only cells expressing IL-2, whereas multiple cell types express IL-15. Differential induction of IL-2R α and IL-15R α is another potential factor. Also, IL-15 binds to IL-15R α alone with far greater affinity than IL-2 binds to IL-2R α alone, so cells expressing both receptors may preferentially bind to IL-15 under conditions where both cytokines are present (18). Finally, the possibility remains that IL-15R α engagement induces IL-2/15R β and γ c signaling events that are quantitatively distinct from those initiated by IL-2R α binding (19). The strength of these signals may then translate into

biologically distinct outcomes for the T cell (e.g., a stronger activation or proliferation stimulus may predispose to programmed cell death).

In summary, the report by Kennedy et al. strongly reinforces the concept that IL-15 performs pleiotropic developmental and homeostatic immune functions, particularly for innate immune cells (7). Curiously, despite the biochemical similarities of IL-2R and IL-15R signals, none of the in vivo biological functions of IL-15 appear to overlap with IL-2's critical role in downregulating activated T cells. The initial findings in IL-15^{-/-} and IL-15R α ^{-/-} mice prompt many new questions about how IL-15 mediates these functions. For example, do all IL-15 signals use IL-15R α , and how are IL-2R and IL-15R signals biochemically distinguished? To what extent does IL-15 support lymphocyte proliferation versus survival? Additional important future directions include understanding IL-15's diverse roles in: NK cell differentiation, activation, and proliferation; NK T cell function; CD8⁺ T cell activation and homeostasis; mucosal immunity; innate and adaptive immune responses; and immunological memory. It will also be important to determine whether IL-15 mediates more subtle functions in CD4⁺ T cells. As these investigations are completed, it may become apparent that IL-15 will encompass far broader biological functions than its scientifically older (but perhaps evolutionarily younger) cousin, IL-2.

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