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Review

Interleukin 15: Its Role in Inflammation and Immunity

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Abstract. Interleukin 15 (IL-15) is a 14–15 kDa polypeptide that belongs to the 4 α-helix-bundle family of cytokines and was originally discovered due to its T cell proliferative activity. It utilizes the signal-transducing β/γ polypeptides of the IL-2 receptor complex, thus sharing many biological activities with IL-2, in addition to its high-affinity private receptor subunit IL-15Rα. Accumulating evidence indicates that the biological relevance of IL-15 may not solely be confined to T lymphocytes, but to a variety of cell populations within the immune system as well as outside the immune system of the host. The expression of both IL-15 and its high-affinity receptor component, IL-15Rα, are readily demonstrable in a wide variety of tissues and appear to be augmented in response to environmental/stress stimuli and infectious agents. There is increasing evidence to suggest that IL-15 may play an important role in protective immune responses, allograft rejection and the pathogenesis of autoimmune diseases, where mononuclear cell infiltration is a hallmark feature. Herein, the effects of IL-15 on cells associated with host defense, immunity and inflammation are reviewed and support a central role for this cytokine in orchestrating multiple aspects of effector functions in immunity and inflammation.

Key words: interleukin 15; natural killer cells; monocytes; dendritic cells.

Introduction

Interleukin 15 is a recently identified cytokine. The discovery of IL-15 was independently reported by two separate laboratories by the detection of an active substance in the culture supernatants of CV-1/EBNA-and HTLV-1-infected HuT-102 cell lines, that had the capacity to stimulate the proliferation of an IL-2-dependent murine T cell line CTLL-2- and was refractory to IL-2-neutralizing antibodies[8, 30]. This novel cytokine, with an approximate molecular weight of 14–15 kDa, is encoded in humans by a single copy gene located on chromosome 4 at band q31, while the murine homolog resides in the central region of chromosome 8 and spans a region approximately 34 kb in length[2]. IL-15 genes in rat[59], simian[30], bovine, porcine and avian species have also been defined and exhibit a high degree of interspecies sequence conservation amongst them (reviewed in refs.[37, 67]).

The original analysis of murine IL-15 genomic structure suggested the presence of 8 exons and 7 introns[2], but more recent studies have revealed the existence of multiple isoforms due to alternate splicing of the primary transcript[30, 45, 53, 65]. Splice variants upon translation generate two different versions of signal peptides, one with 48 amino acids and the other with 21 amino acids, which leads to differential compartmentalization of the cytokine. The 48-amino-acid signal peptide mediates the secretion of IL-15 extracellularly, while the shorter 21-amino-acid signal peptide

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leads to cytoplasmic and, perhaps, nuclear accumulation of IL-15. The coding region for the mature polypeptide remains unmodified in these mRNA isoforms and encodes a 114-amino-acid polypeptide. Interestingly, in a recent study, transgenic mice that express the 48-amino-acid but not the 21-amino-acid signal peptide version of IL-15 displayed markedly increased numbers of $CD44^{high}$ $Ly6C^{+}$ memory-type CD8 T cells in the lymph nodes and heightened resistance to *Salmonella* infection[50].

The presence of an untranslated 5' leader sequence that spans over 350 nucleotides in the human IL-15 mRNA (465 nucleotides in murine IL-15 mRNA), in addition to the sequence elements that encode an unusually long signal peptide, sets it apart from the other cytokines that belong to the 4α-helix-bundle family, which includes IL-2, IL-3, IL-4, IL-5, IL-6, IL-7 and IL-9 (reviewed in refs.[37, 68]). The 3' untranslated region of IL-15 mRNA is approximately 400 nucleotides in length and contains AU-rich regions but their relevance to the stability of IL-15 transcript remains undefined[68].

Unlike IL-2 and many other hematopoietic cytokines that display restrictive tissue expression, the expression of IL-15 mRNA can be readily demonstrated by Northern analyses in a wide variety of tissues and in many cell lines of diverse tissue origin. Analysis of human tissues reveals abundant expression of IL-15 mRNA in skeletal muscle, placenta, kidney, liver, lung, pancreas, brain and in the $CD14^{+}$ monocytes of peripheral blood mononuclear cells[7, 30]. The failure to detect IL-15 mRNA in T and B lymphocytes by Northern analysis reflects the low expression in these cells, since IL-15 expression is demonstrable by more sensitive ribonuclease protection assays (RPA) or by reverse-transcriptase polymerase-chain reactions (RT-PCR) in normal T cells obtained *ex vivo* or in T cell lines[4, 30].

The promoter/upstream region of both the murine and the human IL-15 gene contains multiple potential sequence motifs to recruit an array of transcription factors, including GCF, NF-κB, IRF-1, myb, γIRE, NF-IL6 and αINF-2 (see ref.[68] for a review), although the elements that impart high basal activity to the IL-15 promoter (as reflected by its abundant expression in normal tissues) have not been delineated at present. Nonetheless, a critical requirement for IRF-1 in the induced-expression of murine IL-15 has been established[50, 51]. A similar role has also been implicated for NF-kB in the expression of IL-15[4, 70].

Despite abundant expression of IL-15 mRNA in many cells and tissues, the detection of IL-15 protein by bio-assays or immunoassays has been difficult. This discordance between IL-15 mRNA expression and IL-15 protein production is attributed to a number of features, which include the presence of an unusually long 5' untranslated leader region in the IL-15 transcript that exerts a stringent control over IL-15 production, predominantly at the level of translation (reviewed in ref.[68]). The tight regulation of IL-15 production, may be vital in avoiding detrimental effects to the host due to the proinflammatory effects of this cytokine.

IL-15 Receptors and Signal Transduction

In T lymphocytes and natural killer (NK) cells, the cell types in which the receptor components of IL-15 have been best studied, IL-15 utilizes the IL-2Rβ and IL-2Rγ components[8, 28] but not the private IL-2Rα component of the IL-2 receptor complex, which exclusively binds IL-2. Due to the shared receptor subunits, IL-15 exhibits a spectrum of immune functions that largely overlaps with that of the T cell growth factor IL-2. Although the usage of the β-chain is limited to IL-2 and IL-15, the γ-chain is also utilized by IL-4, IL-7 and IL-9 and is designated as the common γ-chain or γ_c. While IL-15 binds to the heterodimeric β/γ chains with modest affinity (a K_a of ~10^9/M), this binding is sufficient to elicit a functional signal transduction cascade. IL-15 also binds specifically with high affinity (K_a~10^{11}/M) to a 60 kDa type-1 membrane protein, designated IL-15Rα[29].

The structural and genetic topology of IL-15Rα resembles that of IL-2Rα, but, unlike IL-2Rβ and IL-2Rγ, these molecules are not members of the hematopoeitin receptor family. They exhibit features associated with certain complement and cell adhesion molecules that possess protein-binding motifs referred to as SUSHI domains (also known as GP-1 motifs or short consensus repeats). Although IL-15Rα contains a sizable cytoplasmic domain (37 amino acids in the human version), at present there is no evidence to indicate that the engagement of its ligand, IL-15, results in any discernible signal transduction. However, when IL-15Rα associates with the IL-2Rβ/γ dimeric complex, rather than sequestering the ligand from the low-affinity dimeric receptor complex, IL-15Rα forms a high-affinity ternary complex consisting of α, β and γ chains that efficiently transduce the IL-15 signal. Unlike the expression of β and γ_c receptor components, which is limited to cells of lymphoid and myelomonocytic lineage, the expression of IL-15Rα has a wide cellular distribution[29]. IL-15Rα mRNA is abundantly expressed in spleen, heart, lung, skeletal muscle, liver, brain and in a variety of cell lines derived from macrophage, epithe-

lial, bone marrow, lymphocyte and NK origin (reviewed in ref.[28]).

Despite high constitutive levels of IL-15Rα expression, IL-15Rα mRNA can be further augmented by activation stimuli. For example, treatment of monocytes with LPS or interferon γ (IFN-γ) leads to rapid but transient induction of IL-15Rα transcript. Similarly, treatment of T cells with IL-2 or phorbol-myristate acetate (PMA) leads to enhancement of IL-15Rα mRNA levels. An important implication of this wide distribution profile of IL-15Rα expression is that the cells expressing IL-15Rα but not β and γ_c subunits have the potential to be involved in the rapid clearance of circulating IL-15 thus functioning as a decoy molecule. Alternatively, it could also represent an efficient means by which IL-15 is presented to other cells of the immune system. The generation of mice with a targeted disruption of the IL-15Rα gene has clarified the importance of the high affinity receptor complex for mediating physiological functions of IL-15[41]. These mice exhibit normal T and B lymphocyte development, but are markedly lymphopenic as a result of a decreased proliferative capacity and an attenuated homing ability of T lymphocytes to reach peripheral lymph nodes.

The potential existence of yet another receptor system in mast cells which do not respond to IL-2 but proliferate in response to IL-15 has also been reported. This receptor with an apparent molecular weight of 60–65 kDa, has been designated IL-15RX[64].

Signaling events ensuing IL-15 binding to its receptor complex are mediated by the IL-2Rβ/γ_c chains and are, thus, very similar, if not identical to those of IL-2 and involve activation of Jak3 and Jak1 kinases, tyrosine phosphorylation of STAT3, STAT5 and subsequent nuclear translocation of these molecules (see ref.[33] for a review). In addition, the phosphorylation of the Src-related cytoplasmic tyrosine kinases $p56^{lck}$ and $p72^{syk}$, the induction of anti-apoptotic gene bcl-2 and the activation of Ras/Raf/MAP kinase pathway have been reported in T cells upon exposure to IL-15 or IL-2. Following the engagement of the mast cell-specific IL-15RX receptor, the signal transduction is reported to proceed via Jak2 and STAT5[64].

IL-15-Mediated Effects on Cells Associated with Host Defense, Immunity and Inflammation

NK cells are pivotal for both innate and adaptive immunity. Almost 90% of the peripheral blood NK cells display a surface phenotype $CD2^+$ $CD16^+$(F_cRγIII) $CD56^{dim}$ with constitutive expression of IL-2Rβ, and γ_c. The remainder are $CD2^-$ $CD16^-$ $CD56^{bright}$ with constitutive expression of all three subunits of IL-2R (α, β, γ_c) and resembles immature cells derived from long-term cultures of $CD34^+$ hematopoeitic progenitors. Because of the constitutive expression of IL-2/IL-15-signaling receptor complex in NK cells, these cells are responsive to both IL-2 and IL-15 (reviewed in ref.[71]). In NK cells, both IL-2 and IL-15 induce cell proliferation, cytotoxicity, cytokine and chemokine (MIP-1α, TRAIL) secretion. However, there is increasing evidence to implicate IL-15 as exerting a more profound effect on NK cell development, differentiation and maturation than IL-2. Examination of NK cell profiles in mice with targeted disruption of IL-2, IL-2Rα or IL-2Rβ gene reveals a complete absence of NK cell activity in mice with a disrupted IL-2Rβ (needed for IL-15 signaling) gene, while no significant perturbation in NK cell populations was observed in the $IL\text{-}2^{-/-}$ and $IL\text{-}2R\alpha^{-/-}$ mice (reviewed in ref.[71]). Moreover, mice with a targeted disruption of the IL-15Rα gene are devoid of $CD3^-$ NK cells, although they still possess some $CD8^-$ $CD44^{hi}$ $NK1.1^+$ thymocytes, implying an important but dispensable role for IL-15 in NKT cell development[41]. In $IRF\text{-}1^{-/-}$ mice, the absence of NK cells has been attributed not to an anomaly in NK cell progenitors themselves, but to a lack of IL-15 expression in the bone marrow microenvironment that nurtures the progenitor cells[51, 52]. Furthermore, NK cells are grossly reduced in $\gamma_c^{-/-}$ mice[14, 24], although other cytokines, such as IL-2, IL-4 or IL-7, that utilize the common γ chain for signal transduction other than IL-15, do not influence the NK cell profile, as judged from mice with targeted disruption of these genes. Similarly, $Jak3^{-/-}$ mice are profoundly deficient in NK cells and Jak3 is pivotal in IL-15 action (see ref.[13] for a review).

In vitro studies further support the critical role of IL-15 in NK cell biology. $CD34^+$ hematopoietic progenitor cells, when cultured in the presence of IL-15 alone or in combination with stem cell factor (SCF, *c-kit* ligand), proliferate, express NK cell markers and develop ADCC and NK-dependent cytolytic activity. Nonetheless, a large proportion of such cells generated from long-term cultures in the presence of IL-15 display a surface phenotype characteristic of immature cells ($CD2^-$ $CD16^-$ $CD56^{bright}$), implicating that, although IL-15 is both necessary and sufficient for the differentiation of NK cells from uncommitted progenitors, other additional factors are likely to be necessary for the completion of NK cell maturation (reviewed in refs.[37, 47, 69]). Thus, *in vivo* and *in vitro* observations collectively make a compelling argument that, despite the redundancy and pleiotropism of most cytokines,

IL-15 alone plays a critical role in NK cell development and function.

IL-15 is also a potent growth factor for T lymphocytes and this property was pivotal in its discovery. Although all three receptor components (IL-15Rα, IL-2Rβ and IL-2γ) are expressed on T cells, their distribution profiles appear to vary in different subsets. For example, the expression of the IL-2Rβ chain is marginal in $CD4^+$ T cells with a naive phenotype ($CD45RO^-$), which constitute the majority of circulating CD4 cells in humans, and these, as a consequence, respond poorly to either IL-2 or IL-15. In contrast, $CD8^+$ T cells, especially the $CD44^{hi}$ memory subset respond to IL-15 robustly and their surface expression of IL-2Rβ is much higher[18, 63]. Conceivably, these cells respond to both IL-2 and IL-15 and may even, in tandem, potentiate T cell responses, such as cell proliferation, cytokine secretion, induction of activation markers such as CD25, CD95 (Fas), TNF receptor type II, CD30 and CD40L and down-regulation of CD27. However, IL-15Rα$^{-/-}$ mice display striking lymphopenia, which results from decreased cell proliferation and defective homing of lymphocytes to peripheral lymph nodes along with markedly reduced CD8 T cells, NK, NKT and TCR γδ lymphocytes[41].

Further support for the role of IL-15 in the motility and migration of T lymphocytes comes from *in vitro* studies that demonstrate the ability of IL-15 to induce the expression of cell adhesion markers, chemokines and their receptors and uropod formation in T lymphocytes[58, 61]. In addition, the relevance of IL-15 in proinflammatory cytokine secretion and other effector functions of TCR γδ lymphocytes has been confirmed by *in vitro* studies[20, 26]. These observations both *in vitro* and *in vivo*, collectively suggest an important role for IL-15 in lymphocyte biology that cannot be adequately compensated for by IL-2. In this regard, there is evidence that in addition to proliferative signals, IL-15 is also important in inducing cell survival signals, primarily, by enhancing the expression of cellular Bcl-2 and Bcl-x_L, though IL-2 has, in contrast, emerged as a key mediator of activation-induced cell death (AICD) in T cells[20, 15].

B Lymphocytes

Although resting B cells appear to be refractory to IL-15, in human B cells stimulated with PMA or cross-linking surface IgM, IL-15 induces cell proliferation[3] and, in combination with CD40 ligand (CD40L), acts as a potent inducer of polyclonal IgM, IgG_1, and IgA, but not IgG_4 or IgE, secretion.

Monocytes/Dendritic Cells

There is increasing evidence that monocytes/dendritic cells are a major source of IL-15 synthesis. In murine macrophages, optimal induction of IL-15 requires both a priming (IFN-γ) and a triggering (LPS, mycobacteria, *Toxoplasma gondii*) stimulus[25]. In human monocytes/macrophages, there is significant constitutively expressed IL-15 mRNA which can be further induced by a variety of stimuli[16]. Moreover, recent observations indicate the existence of a constitutively expressed, biologically active membrane-bound form of IL-15 on normal human monocytes[49]. Monocyte-derived IL-15, in addition to its paracrine effects on other cells, especially NK and T cells, also exerts autocrine activity by inducing IL-8 and MCP-1 secretion, chemotactic activity[6] and superoxide production[66] that potentially contributes to the monocyte-mediated host defense and innate immunity. $CD34^+$ hematopoietic precursor cells, when cultured in the presence of granulocyte-macrophage CSF and TNF-α, result in dendritic cell development. Similarly, $CD34^+$ progenitors, when cultured for 2–4 weeks in the presence of IL-15 alone, also generate cells with typical morphological, immunocytochemical, phenotypic and functional characteristics of mature dendritic cells[10]. IL-15 appears to be constitutively expressed in various subpopulations of dendritic cells, including Langerhans cells in the epidermis, and its secretion appears to be enhanced by CD40-mediated events[39].

Monocytes/macrophages and dendritic cells constitute the primary antigen-presenting cells (APC) in the body and IL-15 synthesis by these cells may facilitate initial APC/T cell interactions both by T cell recruitment and their activation, resulting in robust proliferative and cytolytic T cell responses[39]. In addition, IL-15 synthesis by endothelial cells appears to promote cell adhesion and the transendothelial migration of specific subsets of activated T lymphocytes into foci of inflammation[54]. IL-15 also enhances the proinflammatory and antifungal activities of polymorphonuclear leukocytes (PMN)[48]. Other cell types in which IL-15 has been demonstrated include epithelial cells, microglial cells, keratinocytes and malignant cells derived from melanomas, rhabdomyosarcomas and lung carcinomas, although the relevance of IL-15, if any, in malignant transformation remains unexplored (reviewed in refs.[37, 68]).

IL-15 and Infectious Diseases

A wide array of infectious agents have been shown to modulate the expression of IL-15 in animal models

or tissue culture systems. Human PBMC infected with Herpes simplex virus, Human herpes virus 6, Human herpes virus 7, Epstein-Barr virus, respiratory syncytial virus, vesicular stomatitis virus, influenza virus, reovirus and Sendai virus all show enhanced IL-15 expression[27]. Tax transcriptional activator of HTLV-1 induces the expression of IL-15 in T cells and this, in turn, may potentially be important in the pathogenesis of HTLV--1-induced disease[4, 72]. Similarly, elevated serum IL-15 levels have been reported in HIV-infected individuals[35] as well as in individuals with hepatitis C infections[36]. Bacterial agents that have been shown to enhance the expression of IL-15 include *Staphylococcus aureus*[17], *Helicobacter pylori*[42] and obligate intracellular pathogens that target monocytes/macrophages, such as *Salmonellae*, *Listeria* and *Mycobacteria*[31, 32, 43]. Elevation of plasma IL-15 has also been reported in melioidosis[40]. Fungal agents, such as *Cryptococcus neoformans*[46], also induce IL-15 expression in monocytes and these cells in the presence of IL-15 display augmented superoxide production and microbicidal activity[66].

IL-15 and Autoimmune Diseases

Immune activation is a hallmark feature in autoimmune and inflammatory disorders. Elevated plasma IL--15 is seen in acquired aplastic anemia[23], moderate to severe ulcerative colitis[38], systemic lupus erythematosus[55] and hepatitis C virus-associated chronic liver disease[36]. In addition, enhanced expression of IL-15 in the infiltrating mononuclear cells are seen in multiple sclerosis[56], sarcoidosis[1], post-transplant heart, liver[5] and kidney biopsies[57]. However, whether the enhanced expression of IL-15 is a surrogate marker that reflects ongoing immune activity or is actually an etiologic component of disease pathogenesis remains an unsettled issue in many of these diseases. Nonetheless, in inflammatory rheumatoid arthritis there is increasing evidence to incriminate IL-15 expressed in synovial--membrane-lining cells to be pivotal in disease pathogenesis[44].

Conclusions and Future Prospects

IL-15, although both genetically and antigenically distinct from IL-2, shares many features with IL-2. They are both members of the 4α-helix-bundle cytokine family and utilize the signal-transducing IL-2Rβ and γ_c receptor subunit for their activity, thus displaying a spectrum of overlapping immune functions: T cell proliferation, activation of cytotoxic effector cells, B cell immunoglobulin synthesis via costimulation, and activation of monocytes. However, evidence from genetically altered mice implies that IL-15 exerts a critical influence particularly on NK and CD8 T cell populations in their differentiation, proliferation and survival, attesting to its importance in both innate and adaptive immune responses of the host that cannot be adequately compensated for by IL-2.

The concept of immune enhancement as a viable option in the management of certain malignancies and immunodeficiencies appears to be promising. Inclusion of IL-2 in conjunction with antiretroviral agents in the treatment of HIV infection continues to yield encouraging results[21]. The effectiveness of IL-2 in treating renal cell carcinoma and malignant melanoma has been established[22]. However, one potential complication of exogenous administration of IL-2 is the vascular leakage syndrome. In this regard, vascular leakage effects of IL-15 are minimal and this, coupled with the observation that IL-15 was still capable of correcting the impaired proliferative response of $CD4^+$ lymphocytes from HIV-infected individuals without the mitogenic effect of IL-2[17] that could trigger HIV replication, provide a rational basis to explore the efficacy of IL-15 as an alternative to IL-2 usage in such circumstances. Furthermore, accumulating evidence indicates incorporation of immunostimulants in various vaccine formulations, either by co-delivery or co-expression, to invoke superior immune responses[62]. IL-15, with its potent effects on both antigen-presenting cells as well as immune effector cells, may prove to be an ideal candidate in such vaccine endeavors. In addition, in chronic inflammatory diseases, such as inflammatory rheumatoid arthritis, and, perhaps, in autoimmune diseases, such as inflammatory bowel disease and sarcoidosis, IL-15 may play a key role in the perpetuation of inflammation. In fact, in an experimental model for rheumatoid arthritis, arthritogenesis can completely be resolved by inhibiting IL-15 activity[60]. There is also evidence to imply that IL-15 may play a causal role in allograft rejection by virtue of its effects on T and NK cells. Thus IL-15 or, alternatively, IL-15 receptors, may offer potentially effective therapeutic targets in the treatment of chronic inflammatory conditions and organ transplantation protocols.

Addendum. Mice genetically deficient in IL-15 (IL-$15^{-/-}$ mice) have been generated recently[36] and these mice display marked reductions in numbers of thymic and peripheral NK T cells, CD8 memory T cells and subpopulations of intestinal intraepithelial lymphocytes in addition to a complete lack of NK cells.

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