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Molecular Pathways: Interleukin-15 Signaling in Health and in Cancer

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Abstract

Interleukin-15 (IL-15) is a pro-inflammatory cytokine involved in the development, survival, proliferation and activation of multiple lymphocyte lineages utilizing a variety of signaling pathways. IL-15 utilizes three distinct receptor chains in at least two different combinations to signal and exert its effects on the immune system. The binding of IL-15 to its receptor complex activates an 'immune-enhancing' signaling cascade in natural killer cells and subsets of T cells, as well as the induction of a number of proto-oncogenes. Additional studies have explored the role of IL-15 in the development and progression of cancer, notably leukemia of large granular lymphocytes, cutaneous T-cell lymphoma and multiple myeloma. This review provides an overview of the molecular events in the IL-15 signaling pathway and the aberrancies in its regulation that are associated with chronic inflammation and cancer. We briefly explore the potential therapeutic opportunities that have arisen as a result of these studies to further the treatment of cancer. These involve both targeting the disruption of IL-15 signaling as well as IL-15-mediated enhancement of innate and antigen specific immunity.

Background

Cytokines play a critical role during the host's immune response against infectious pathogens and malignant transformation. One such cytokine, interleukin-15 (IL-15), is central to the development, survival and activation of natural killer (NK), T-, and B-cells (1–5). Discovered in 1994, IL-15 is a member of the 'four α-helix bundle' cytokine family that signals via the common gamma (γ) chain and the IL-2 receptor (R) beta (β) chain, and as a result the two cytokines share select biological functions (6–8). Here we will discuss the structure, regulation and biological functions of IL-15 in a wide variety of cell lineages as well as its role in genesis of cancer.

The human and mouse *IL15* gene have approximately 73% sequence homology and are mapped on chromosome 4 and 8, respectively (9). The DNA sequence of the human IL-15 gene consists of six protein-coding exons and five introns compared to eight exons and seven introns in the mouse (9, 10). The presence of two different signal peptides (SP) in the

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IL-15 gene results in alternative splicing and the subsequent generation of two IL-15 isoforms in both human and mouse (11). While both the long (LSP) and short (SSP) isoforms produce mature proteins, they each have distinct intracellular trafficking, localization and secretion patterns (11, 12). The LSP isoform is primarily located in the Golgi apparatus, early endosomes, and endoplasmic reticulum and is often secreted from the cell as a soluble protein. The SSP isoform is confined to the cytoplasm and nucleus suggesting its role as a transcriptional regulator (11–16).

IL-15 transcript is abundantly produced by a large variety of tissues and cell types: (a) tissues include the placenta, skeletal muscle, kidney, lung and heart tissue; (b) cell types include epithelial cells, fibroblasts, keratinocytes, nerve cells, monocytes, macrophages, and dendritic cells (6, 17–20). Transcriptional activation of IL-15 occurs via the binding of NF-κB and IRF-E to the 5′ regulatory region of IL-15, amongst other active motifs such as GCF, myb and INF2 (20–26). Despite the abundant expression of IL-15 transcript, IL-15 protein is stringently controlled and expressed primarily within monocytes, macrophages and dendritic cells (6, 17, 18). This discrepancy between IL-15 transcript and protein expression is due to complex translation and intracellular protein trafficking culminating in barely detectable levels of the protein *in vivo*. IL-15 post-transcriptional checkpoints include a complex 5′-UTR containing: (a) multiple AUG sequences upstream of the initiation codon; (b) a C-terminal negative regulatory element; and (c) an inefficient signal peptide (12, 14, 17, 23, 27). Collectively, these mechanisms serve to limit IL-15 protein production and secretion from its vast stores of transcript.

Despite the lack of homology in the amino acid sequence between IL-15 and IL-2, the mature IL-15 protein binds to the IL-2Rβγ heterodimer, activating the intracellular signal leading to cell activation (6, 7, 28, 29). The third component of the IL-15R complex is a unique α-chain (IL-15Rα). In contrast to the IL-2Rα chain that binds IL-2 with low affinity and confers high affinity for IL-2 only when non-covalently linked the IL-2Rβγ complex, IL-15Rα is by itself a high affinity receptor for IL-15 (30). Once IL-15 is secreted out of the cell, it binds to either the membrane bound or the soluble form of IL-15Rα and is presented *in trans* to and bound by the IL-2Rβγ complex expressed on nearby effector cells in order to initiate cellular activation (31).

IL-15 utilizes select Janus-associated kinases (JAK) and signal transducer and activator of transcription (STAT) proteins as a means of initiating signal transduction for cellular activation (32). In lymphocytes, binding of IL-15 to the IL-2/15Rβγ heterodimer induces JAK1 activation that subsequently phosphorylates STAT3 via the β chain and JAK3/STAT5 activation via its γ chain (33, 34) (Figure 1). Phosphorylated STAT3 and STAT5 proteins form heterodimers that then translocate to the nucleus where they activate transcription of the anti-apoptotic protein bcl-2 and proto-oncogenes c-myc, c-fos, and c-jun (26, 35–37). Mice that have genetic disruption of IL-15, JAK3 or STAT5 show a profound lymphoid cell deficiency (4, 38–40).

Akt is activated via a phosphatidylinositol 3-kinase (PI3K)-dependent pathway, and in lymphocytes this occurs despite the absence of PI3K binding sites on the IL-2/15Rβγ (41, 42). The signaling mechanism utilizes an adaptor protein, Shc, which binds to a

phosphotyrosine residue on the IL-2/15Rβ resulting in activation of Grb2 and onto AKT via the Shc→Grb2→Gab2→PI3K→Akt signaling pathway to increase cell proliferation and/or survival (41) (Figure 1). In a third signaling pathway that follows the trans-presentation of IL-15 to IL-2/15Rβγ and Shc-mediated activation of Grb2, the latter binds to the guanine nucleotide exchange factor SOS to form a Grb2-SOS complex that then activates the Ras-Raf pathway by facilitating the removal of GDP from a member of the Ras subfamily that in turn activates the mitogen-activated protein kinase (MAPK) pathway for cellular proliferation (Figure 1) (43, 44). Thus IL-15-mediated Grb2 phosphorylation regulates both the PI3K and MAPK pathways. Collectively, these signaling mechanisms induce expression and activation of downstream effector molecules such as c-myc, c-fos, c-jun, Bcl-2 and NF-κB (36).

In contrast to lymphocytes, mast cells utilize the express a distinct receptor, termed IL-15RX to activate the JAK2/STAT5 pathway (45). Murine mast cells treated with IL-15 appear to engage the IL-2/15Rγ chain to induce rapid phosphorylation of Tyk2/STAT6 for initiation of a Th2 type immune response (46) (Figure 1). In neutrophils, IL-15 has been shown to upregulate the anti-apoptotic gene Mcl-1 through the MAPK pathway (47, 48).

Functionally, IL-15 supports cell expansion and maintenance by: (a) inducing strong proliferative signals via JAK/STAT and Ras/MAPK signaling pathways, and (b) preventing cell death by increasing anti-apoptotic proteins Bcl-2 and Bcl-xL as well as decreasing pro-apoptotic proteins Bim and Puma through activation of PI3K pathway (24, 32, 33, 36, 43, 44). Additionally, IL-15 enhances the cytotoxic effector functions of lymphocytes by increasing production of a cytolytic pore forming protein, perforin, and death-inducing enzymes, granzymes A/B, through all three pathways (39, 40, 49). IL-15 signaling is also well known to evoke a Th1 immune response by inducing release of IFNγ and TNFα; however, it can also trigger a Th2 response through release of IL-4 and IL-5 in activated human T-cells (50, 51). Similarly, in mast cells and monocytes, IL-15 induces the release of IL-4 and the chemokine IL-8, respectively (46, 52). In addition to increasing expression of chemokine receptors in lymphocytes, IL-15 is a potent chemoattractant, thus inducing infiltration of T- and NK cells at the site of its production (53, 54).

Clinical-Translational Advances

Targeting IL-15 in cancer

The anti-tumor effect of IL-15 on the immune system has been well documented in experimental systems (55) nonetheless, accumulating evidence suggests IL-15 can also initiate and promote certain types of malignancies.

Multiple myeloma (MM) is a disease characterized by the accumulation of malignant plasma cells in the bone marrow, and is particularly sensitive to IL-15 signaling. Exploring expression patterns of the IL-15R subunits in six MM cell lines, as well as in the neoplastic cell fraction of fourteen MM patients, Tinhofer and colleagues found that malignant plasma cells expressed all three components of the IL-15R heterotrimer (56). While healthy B-cells from normal donors downregulate IL-15Rα in response to IL-15, MM cells do not exhibit such a reduction in response to IL-15 stimulation. *In vitro*, IL-15 overexpression in

malignant plasma cells protects them from spontaneous apoptosis as well as a broader range of activation induced cell death (56). These data suggest that MM cells can inhibit apoptosis and sustain themselves via autocrine IL-15 stimulation, thereby becoming less dependent upon their microenvironment. Further studies, however, are needed to elucidate the cellular mechanisms of IL-15 mediated signaling in MM pathogenesis.

IL-15 is a growth and viability factor for malignant T cells in cutaneous T-cell lymphoma (CTCL), a lymphoproliferative disorder characterized by migration and expansion of malignant CD4+ T-cells in the skin (57). Skin lesion and peripheral blood T cells of CTCL patients show over-expression of IL-15 mRNA and protein (57, 58). Although not yet directly proven, IL-15 is thought to play an important role in the epidermotropism found in CTCL, given its aberrant expression in the skin of these patients and its strong chemoattractive properties for T-cells (57, 59). IL-15 expression data from CTCL patients strongly supports the notion that in the early stages of CTCL, survival of malignant CD4+ T-cells is dependent on IL-15 supplied from the microenvironment, but as the disease progresses, malignant cells may sustain their own growth through autocrine IL-15 production and signaling. More importantly, IL-15 mediated JAK1 and JAK3 phosphorylation results in constitutive STAT activation that contributes significantly to the growth and survival of malignant T-cells in CTCL patients (60, 61). Of note, exposure of CD4+ CTCL cells to IL-15 results in increased expression of anti-apoptotic bcl-2 via the upregulation of STAT5 and c-myb, suggesting a protective mechanism of cell survival that is not present in non-malignant CD4+ cells (62). Collectively, these results suggest that IL-15 likely plays a role in the pathogenesis of CTCL, acting as a potent chemoattractant of T-cells to the skin, as a paracrine and autocrine survival and growth factor for malignant cells as well as an inhibitor of activation induced cell death.

IL-15 was co-discovered in the Waldmann laboratory while studying the human T-cell lymphocytic virus (HTLV-1)-infected T cell line, HUT102, in the absence of IL-2 (7, 63). It was subsequently learned that the Tax protein of the virus induced the infected T-cells to express both IL-15 and IL-15Rα. Thus, IL-15–mediated autocrine growth led to transformation of HTLV-1-associated adult T-cell leukemia/lymphoma (20, 63).

Patients with leukemia of large granular lymphocytes (LGLs) show increased serum levels of soluble IL-15Rα and constitutive expression of the IL-2/15Rβγ and membrane-bound form of IL-15 in leukemic blasts (64, 65). These data, and the fact that IL-15 is critical for the development and survival of both normal LGL (5, 66) and their malignant counterparts (67), support a role of IL-15 in LGL leukemia. Notably, two human LGL cell lines established from patients with CD3- LGL leukemia show requirement of IL-2 or IL-15 signaling via the IL-2/15Rβγ for survival and proliferation *ex* vivo (68, 69). While short-term exposure of IL-15 causes enhanced proliferation, cytokine production and cytotoxic functions in normal LGLs (32–34, 39, 40), chronic IL-15-mediated activation via the JAK/STAT pathway, especially STAT3 and STAT5, can be leukemogenic. Somatic mutations in the SH2 domain of STAT3 have been discovered at the frequency of 40% in T-LGL leukemia and 30% in NK-LGL leukemia patients (70, 71). Unprecedented in the cancer genome, a novel somatic mutation in the STAT5b gene has been discovered in 2% of patients with aggressive LGL leukemia (72). Since IL-15 signaling and STAT3/STAT5b

somatic mutations increase transcriptional activity of STAT proteins, the evidence suggests that the IL-15 signaling pathway is critical for the genesis of LGL leukemia. Indeed, transgenic mice engineered to overexpress IL-15 develop spontaneous T- and NK-LGL leukemia that exhibit hallmarks of the human disease (73, 74). More importantly, chronic exposure to IL-15 alone is sufficient to initiate malignant transformation of wild type mouse LGL through two distinct pathways, both of which are regulated by IL-15-mediated induction of Myc (75). In the first cascade, IL-15 mediates 'Myc'-induced overexpression of aurora kinase A and B, resulting in centrosome amplification and consequent chromosomal instability. In the second pathway, Myc induces the downregulation of *microRNA (miR)-29b*, which in turn increases the expression of DNA methyltransferases and the methylation of genomic DNA, furthering chromosomal instability and silencing key tumor suppressor genes (75).

Proteasome inhibition by bortezomib impairs the *miR-29b*-mediated signaling cascade by inhibiting binding of the 'Myc/NF-κB/Hdac1' co-repressor complex at the *miR-29b* promoter (76). It is noteworthy that IL-15 reduces expression of the pro-apoptotic protein 'Bid' in LGL leukemia via a proteasome dependent mechanism, thereby protecting malignant cells from apoptosis, which can be reversed by blocking both IL-15 and IL-15Rα. In human LGL leukemic cells, induction of Bid by the proteasome inhibitor bortezomib increased leukemic cell death, suggesting this could be an effective treatment option for this disease (77). Furthermore, *in vivo* administration of a novel formulation of bortezomib cured this otherwise fatal malignancy in mice with late stages of the disease (75), thus offering a new approach to treating patients with aggressive LGL leukemia.

Another therapeutic approach has been to use monoclonal antibody Mikβ1 to block presentation of IL-15 to the IL-2/IL-15Rβ thereby inhibiting proliferation of an IL-15 dependent cell line, Kit-225, *in vitro*. Though successful *in vitro*, clinical trials with Mikβ1 antibody (both mouse and humanized antibody) have thus far not produced notable clinical responses in patients with LGL leukemia (78, 79). In a recent Phase 1 clinical trial, a total of nine CD3+CD8+CD122+ T-LGL leukemic patients were treated with single intravenous dose of 0.5, 1.0 or 1.5 mg/kg of Mikβ1 (3 patients/group), and showed neither antibody associated toxicity nor clinical response (78). A Phase I-II clinical trial utilizing the same antibody in patients with fatal HTLV-1-associated T-cell leukemia is ongoing (NCT00076843) (80). Finally, as a variety of STAT3 inhibitors come forth to the clinic, it will be important to screen LGL leukemia patients for STAT3 mutations for inclusion in early phase clinical studies (81).

IL-15 in clinical cancer therapy

Early trials in several solid tumors are showing remarkable clinical responses in patients who are treated with agents that block negative regulators of T cell activation i.e. CTLA-4 and PD-1 (82–84). Likewise, transplantation of haploidentical, KIR-ligand mismatched, T-cell depleted stem cells to patients with acute myeloid leukemia has yielded promising results (85). In both instances, it is likely that the critical effector lymphocyte populations (i.e., cytotoxic T cells and NK cells, respectively) are activated by IL-15, which is now in several Phase I clinical trials as a single agent (NCT01385423, NCT01572493,

NCT01369888, NCT01875601 and NCT01021059) (80). Thus, once a proper dosing and delivery schedule are achieved with IL-15, a combination with these immunologic checkpoint inhibitors will hopefully be investigated to further improve response rates without exacerbating auto-reactivity against non-malignant tissues. The soluble IL-15Rα-IL-15 dimer is also in clinical development and might offer enhanced pharmacodynamic and pharmacokinetic properties over IL-15 alone (86). In contrast to IL-2, IL-15 does not appear to expand regulatory T-cells that exert an immunosuppressive effect (87–89). Experimental studies comparing the two cytokines *in vivo* would suggest a significant difference in the anti-tumor potency mediated by T-cells that favors IL-15 (55).

Conclusions

IL-15 is an important cytokine in the regulation of the normal host immune response and thus likely has a role in protection against pathogens and malignant transformation. The molecule utilizes a variety of signaling pathways to control lymphocyte development, survival, proliferation and activation. Chronic stimulation can lead to malignant transformation of T and NK cells in experimental systems and clinical data from patients with CTCL, HTLVI and LGL leukemia appear to support its oncogenic properties. Harnessing IL-15's powerful properties to enhance lymphocyte effector function in the setting of malignancy is likely to take shape over the next decade, leading to its broad use in the treatment of both hematologic and solid tumor malignancies.

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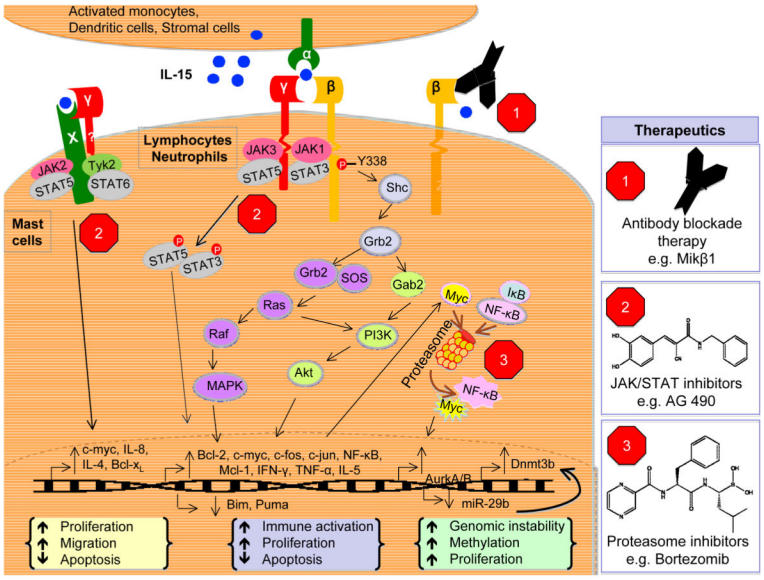

Figure 1. Intracellular signaling of IL-15

In one scenario (right), IL-15 binds to its high affinity IL-15Rα expressed on an antigen-presenting cell and in turn is presented *in trans* to the IL-2/15Rβγ heterodimer. From there, effector cell activation can proceed via three distinct pathways: one involves JAK-STAT activation with the phosphorylated STAT proteins forming a heterodimer and trafficking to the nucleus for transcriptional activation; a second pathway involves the recruitment of Shc to a phosphorylated site on the IL-2/15Rβ chain followed by activation of Grb2. From there, Grb2 can proceed down a PI3K pathway to phosphorylate Akt, or can bind the guanine nucleotide exchange factor SOS to activate RAS-RAF and ultimately MAPK. Each contributes to effector cell survival and activation.

In mast cells (left), IL-15 signals through a unique receptor chain, IL-15RX, to activate the JAK2/STAT5 pathway. IL-15 can also bind to the common γ chain to transmit its signals via Tyk2/STAT6 for initiation of a survival (Bcl-X_L) and a Th2 immune response. Therapeutic interventions using anti-IL-15R antibody prevents binding and signaling of IL-15 through its receptor. Pharmacological inhibitors targeting the JAK/STAT pathway prevent activation and translocation of the STAT heterodimer to the nucleus. Finally, proteasomal inhibitors such as bortezomib prevent activation of NF-κB and Myc. Each of these therapies targets IL-15 signaling in malignant cells, but may have consequences for normal cells dependent upon IL-15.