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UDC 571.27; 619 **Review article**

Effects of interleukin-15 on bovine natural killer and CD8+ T cells and its potential in treating viral infections

Kanatbek N. Mukantayev[1], Kanat A. Tursunov[1], Zhansaya B. Adish[1,2], Darkhan B. Kanaev[1], Laura A. Tokhtarova[1], Malika Nurtleu[1], Bisultan E. Abirbekov[1]

[1]Laboratory of Immunochemistry and Immunobiotechnology, National Center for Biotechnology, Astana, Kazakhstan,
[2]Department of Natural Sciences, L.N. Gumilyov Eurasian National University, Astana, Kazakhstan

Corresponding author: Kanat A. Tursunov: kanat_tka@mail.ru
Co-authors: (1: KM) mukantaev@biocenter.kz; (2: ZA) zhansaya.adish@gmail.com; (3: DK) dake_2008z@mail.ru; (4: LT) laura_2626@mail.ru; (5: MN) malika.nurtleu@gmail.com; (6: BA) abirbekovbisultan@gmail.com
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Abstract

Interleukin-15 (IL-15) is a promising cytokine for immunotherapy of human cancers and bovine viral infections. IL-15 indirectly has a negative effect on tumor and virus-infected cells by activating the signaling pathways of proliferation and activation of natural killer (NK) and memory CD8+ T cells. IL-15 therapy may have widespread clinical use, particularly when combined with chimeric antigen receptor (CAR) T or CAR NK cells. Additionally, the use of IL-15 in combination with checkpoint inhibitors and other therapies holds promise as a treatment for cancer and viral infections. Understanding the biological characteristics of IL-15 is crucial for developing effective therapeutic strategies. This study aimed to explore recent advances in IL-15 research, focusing on its antitumor mechanisms within the tumor microenvironment, advances in IL-15-based therapies for bovine viral infections, and its integration with other treatment approaches, including monoclonal antibodies.

Keywords: cancer; cytokine; immunotherapy; interleukin-15; natural killer cells; viral infection.

Introduction

Interleukins (ILs) are biologically active protein molecules that regulate immune and inflammatory responses in the body. They activate signaling pathways in immune cells and coordinate their interactions to defend against infections, diseases, and tissue damage. ILs promote immune cell growth, differentiation, and survival while stimulating phagocytes to eliminate pathogens [1, 2, 3]. ILs exert paracrine or autocrine effects on target cells by binding to specific receptors [4]. A notable characteristic of ILs is their self-limiting nature, which is driven by the instability of most mRNAs, resulting in shortterm synthesis and rapid protein secretion [3, 4].

ILs are classified based on their genetic sequences and functional activities. More than 40 types of ILs have been identified and categorized into several families. The IL-1 family, including IL-1α and IL-1β, plays an important role in inflammatory processes and immune cell activation [5]. The IL-2 family, including IL-4, IL-7, IL-9, IL-15, and IL-21, regulates the growth and differentiation of T, B, and natural killer (NK) cells [6, 7]. The IL-6 family, including IL-6 and IL-11, plays a role in inflammatory processes and immune response regulation [8]. The IL-10 family, including IL-10, IL-19, and IL-20, exhibits anti-inflammatory properties by reducing the activity of macrophages and other immune cells [9]. The IL-12 family, including IL-12, IL-23, and IL-27, contributes to T-helper cell activation and adaptive immune response modulation [10]. The IL-17 family, including IL-17A-F, is a critical inflammatory mediator that activates neutrophils and promotes inflammatory disease [11]. IL-18 and IL-33 are involved in the inflammatory response and pathogenesis of allergic diseases [12]. Each

family fulfills specific functions to maintain the balance of the immune system, protect the body against infections, and regulate inflammatory and autoimmune responses.

The functions of ILs have attracted attention as potential therapies for viral infections in farm animals, including bovine leukemia virus (BLV) [13]. BLV-infected cows exhibit impaired cytokine production, reduced T cell proliferation, and increased T cell apoptosis. They exhibit elevated levels of transforming growth factor-β and IL-10 and decreased levels of gamma interferon (IFN-γ), IL-12, IL-2, and IL-4. The increase in IL-10 levels promotes the expansion of regulatory B and T cells, leading to the suppression of the immune system and reduced ability to combat infection [14].

IL-15 and the representatives of the related family play an important role in effector T cell proliferation and longterm immune response formation. The expression of this cytokine contributes to the increase in the number of memory CD8+ T cells and maintenance of their activity. *Ex vivo* and *in vivo* experiments have shown that IL-15 increases the proliferation of T cell precursors in mice with chronic viral infections. Furthermore, IL-15 combined with anti-programmed cell death 1 (PD-1) antibodies has been reported to significantly promote the development of infection via the activation of CD8+ T cells, and IL-15 combined with anticancer monoclonal antibodies (mAbs) significantly enhances antibody-dependent cellular cytotoxicity, thereby increasing the effectiveness of the therapy [15, 16].

The aim of this study was to analyze the latest advances in IL-15 research, focusing on its antitumor mechanisms within the tumor microenvironment, its application in the treatment of viral infections in cattle, and its integration with other therapeutic approaches, including monoclonal antibodies.

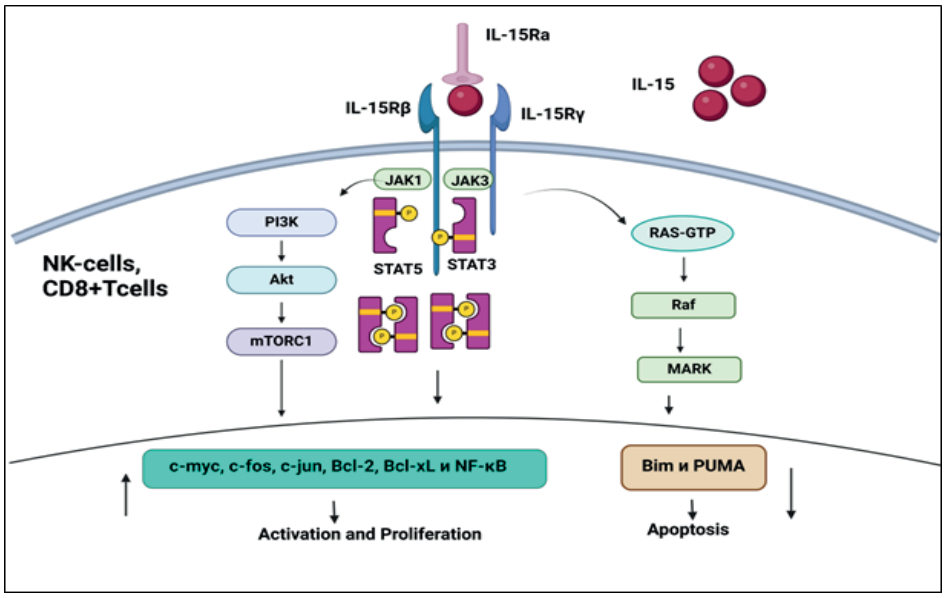
Biological functions of IL-15

IL-15 is synthesized by various cells, including macrophages, fibroblasts, epithelial cells, and endothelial cells, and plays a critical role in various biological processes. It plays a role in immune system regulation by activating and enhancing the survival of NK cells. IL-15-activated NK cells exhibit increased proliferation and functionality, whereas the combined use of IL-15 and IL-18 enhances their survival, maintains phenotypic properties, and increases the expression of the anti-apoptotic Bcl-2-like protein 1 [17]. IL-15 combined with IL-12 more effectively induces the production of cytokines, such as IL-10, MIP-1α, MIP-1β, and TNF-α, while slightly increasing IFN-γ levels. Previous studies have shown that the maximal production of granulocyte-macrophage colony-stimulating factor is achieved with a combination of IL-15 and IL-18 [18].

In addition to promoting the proliferation and activation of NK cells, IL-15 stimulates the activation and proliferation of various T-lymphocyte subsets, including $CD8^{-}CD4^{-}$, $CD8^{+}CD4^{+}$, $CD8^{+}$, and $CD4^{+}$ T cells. The proliferative effects of IL-15 are observed at all stages of $CD8^{+}$ T-lymphocyte development, primarily due to the increased expression of the anti-apoptotic molecule Bcl-2. Additionally, IL-15 enhances the induction of the anti-apoptotic protein Bcl-2 in exhausted $CD4^{+}$ T cells and Bcl-2 and Bcl-xL in activated $CD4^{+}$ T cells and memory $CD8^{+}$ T lymphocytes [19, 20]. Like IL-2, IL-15 activates the intracellular signaling pathways JAK1/STAT3 and JAK3/STAT5 by binding to the IL-2Rβ/γc receptor. These pathways subsequently trigger additional cascades, including PI3K/AKT/mTOR, Ras/Raf/MAPK, and AKT-XBP1s, which promote the expression and activation of key factors, such as c-myc, c-fos, c-jun, Bcl-2, Bcl-xL, and NF-κB. Concurrently, IL-15 reduces the expression of pro-apoptotic molecules such as Bim and PUMA (Figure 1). These effects enhance the survival, proliferation, and activation of effector T cells [20, 21, 22]. Unlike IL-2, which supports the proliferation of regulatory T (Treg) cells, IL-15 exerts minimal effects on Treg cells. This distinction is significant because Treg cells expressing FOXP3 inhibit effector T cells, thereby suppressing immune responses [23].

In addition to maintaining the balance of the immune system, IL-15 plays a key role in T cell activation in various inflammatory conditions. In viral and bacterial infections, signals from Toll-like receptors or type I interferons stimulate the production of IL-15 in antigen-presenting and epithelial cells [24]. IL-15 activates memory $CD8^{+}$ T cells, promoting their proliferation and effector functions in the absence of T cell receptor stimulation. In viral infections, elevated IL-15 levels promote the polyclonal expansion of memory $CD8^{+}$ T cells with diverse receptor repertoires. Although some studies have reported the protective role of IL-15, others have shown its potential to cause host tissue damage in bacterial infections [25, 26]. This pathological effect is evident in acute hepatitis A virus infection, in which elevated IL-15 levels stimulate NK-like cytotoxic activity in $CD8^{+}$ T cells, targeting liver

hepatocytes [27, 28]. Genetic variations in IL-15 or its receptor IL-15Rα are associated with an increased risk of autoimmune diseases, even in the absence of infection [29, 30]. Additionally, IL-15 activates the PI3K/AKT pathway, thereby maintaining chronic inflammation [31, 32, 33, 34].



Upon binding to its high-affinity receptor IL-15Rα and subsequent presentation to the IL-2/15Rβγ heterodimer, IL-15 triggers the activation of effector cells through three primary pathways: (1) the JAK-STAT pathway; (2) the PI3K-AKT pathway; and (3) the Ras-Raf-MAPK pathway.
Figure 1 – IL-15 signaling pathways in effector cells

Furthermore, IL-15 has been shown to enhance the effectiveness of antitumor mAbs and stimulate the secretion of the XCL1 chemokine and IFN-γ in activated NK and $CD8^+$ T cells. XCL1 facilitates the recruitment of type I dendritic cells to tumor tissues, whereas IFN-γ provides positive feedback to strengthen immune surveillance against tumors [30, 35, 36]. Additionally, IL-15 can stimulate memory $CD8^+$ T cells by upregulating Cpt1a expression [19, 37]. The Cpt1a enzyme catalyzes the transfer of long-chain acyl groups from acyl-CoA to carnitine, thereby allowing the entry of fatty acids into the mitochondrial matrix, where β-oxidation occurs [37]. This metabolic function of IL-15 highlights its potential application in combating obesity and metabolic disorders [37, 38].

IL-15 has tremendous antiviral and antitumor potential, making it a promising candidate for immunotherapy. In oncology, IL-15 holds therapeutic promise due to its ability to activate NK and $CD8^+$ T cells, enhance their antitumor activity, stimulate the recruitment and activation of dendritic cells, and establish a positive feedback loop to sustain immune surveillance against tumors.

Clinical significance of IL-15

IL-15 is a promising therapeutic agent for treating cancer and viral diseases. However, its clinical application is limited due to insufficient data on its systemic effects [39]. Two main approaches have been proposed to address these challenges: the first involves modifying the structure of IL-15 itself, and the second focuses on developing IL-15/IL-15Rα complexes [22]. Several IL-15-based therapeutics have been successfully developed and evaluated in clinical trials [40].

SO-C101 is a recombinant protein consisting of IL-15 fused with the NH_2-terminal (amino acids 1–77, $Sushi^+$) domain of IL-15Rα. This fusion extends the protein's half-life and promotes NK cell development and differentiation. Preclinical studies in a mouse model of colorectal cancer have shown that SO-C101 exhibits enhanced antitumor activity when combined with anti-PD-1 agents. This effect is mediated by the stimulation of $CD8^+$ T cell proliferation and activity in vivo. Additionally, SO-C101 promotes tumor cell killing and reduces metastasis by increasing NK cell infiltration, maturation, and proliferation while decreasing neutrophil infiltration in the lungs. Phase 2 clinical trials have evaluated the efficacy and safety of the combination of SO-C101 and the PD-1 inhibitor pembrolizumab in patients with advanced solid tumors and revealed clinical benefits and an encouraging safety profile [4, 41].

HetIL-15 (NIZ985) is a recombinant isomer of IL-15 and IL-15Rα, resembling IL-15 found in human plasma. Several studies in mice and macaques have shown that HetIL-15 has favorable pharmacokinetic properties and promotes cytotoxic lymphocyte proliferation. Additionally, a study on pancreatic adenocarcinoma showed that HetIL-15 therapy promoted tumor growth suppression, prolonged survival, and enhanced sensitivity to chemotherapy [42, 43].

SHR-1501 is a recombinant IL-15 engineered to enhance its activity via conjugation with IgG1-Fc. This modification extends the protein's half-life and stimulates T, B, and NK cell proliferation. To date, two phase I clinical trials have been conducted in China and Australia to evaluate the safety and efficacy of SHR-1501 in patients with advanced tumors [44].

NKTR-255 is a conjugate of two rhIL-15 proteins linked via polyethylene glycol that can interact with IL-15 receptors while retaining its biological properties. With its extended half-life and high potency, NKTR-255 induces the sustained activation and proliferation of NK cells and CD8+ T cells, thereby enhancing antitumor activity, including significant effects in multiple myeloma [45, 46].

HCW9201 is an IL-15 agonist consisting of a fusion protein that targets IL-12, IL-15, and IL-18 receptors. It activates and sustains memory NK cells while boosting their antitumor function. HCW9201 is currently used to treat leukemia and has been shown to enhance short- and long-term NK cell cytotoxicity and IFN production against leukemia cells [47].

ALT-803, also known as N-803, is an IL-15/IL-15Rα tetramer formed by fusing two IL-15 mutants (IL-15 N72D) with two IL-15Rα Su-IgG1 Fc fusion proteins. Phase I clinical trials have confirmed the tolerability and potential efficacy of a once-weekly dosing regimen of ALT-803 [22, 48].

Given its positive effects on the proliferation of NK cells and memory CD8+ T cells, IL-15 has attracted interest as a potential treatment for bovine leukemia. The combination of IL-15 and immune checkpoint inhibitors is a promising therapeutic approach. Combining IL-15 with anti-PD-L1 and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies significantly improved survival rates in mouse tumor models [49]. Currently, cytokines are being studied in conjunction with other forms of immunotherapy. Various formulations of IL-15 may demonstrate enhanced efficacy when combined with anti-CTLA-4 and anti-PD-L1 antibodies, as these combinations have shown highly effective antitumor responses [50]. This treatment strategy can significantly increase the numbers of NK and memory CD8+ T cells. Several preclinical studies have shown that the combination of IL-15 and anti-PD-L1 and anti-CTLA-4 antibodies markedly improves antitumor immunity, reduces tumor growth, and increases survival rates [50, 51].

Based on these findings, we conducted experiments to evaluate the synergistic effect of recombinant bovine IL-15 (rbIL-15) with mAbs targeting CTLA-4 and PD-L1 on IFN-γ production. No statistically significant increase in IFN-γ levels was observed in peripheral blood mononuclear cells (PBMCs) from healthy cows treated with mAbs and rbIL-15 compared with rbIL-15 alone. In PBMCs from BLV-positive cows, the triple combination significantly enhanced IFN-γ production compared with the other groups. Interestingly, no differences in IFN-γ levels were observed between healthy and BLV-positive cows treated with rbIL-15 alone. Despite these findings, the in vitro results are insufficient to justify the practical application of combination therapy in BLV-positive cattle. Therefore, further studies are needed to analyze the effects of IL-15 on T and B cells both *in vitro* and *in vivo*. These studies will provide valuable insights into using IL-15 as a molecular adjuvant to enhance the intensity and duration of immune responses [20].

The ability of IL-15 to stimulate the key mechanisms of innate and adaptive immunity significantly enhances the resistance of farm animals to viral infections. This property is particularly valuable in environments with high housing densities and high risks of epizootics. IL-15 stimulates the proliferation and cytotoxic activity of NK cells, serving as the first line of defense against viruses. This function is especially critical for combating infections, such as African swine fever, highly pathogenic avian influenza, porcine reproductive and respiratory syndrome, and classical swine fever. Additionally, IL-15 promotes the survival and activation of cytotoxic T lymphocytes, which recognize and eliminate virus-infected cells. IL-15 also induces the production of interferons, such as IFN-γ, thereby enhancing cellular resistance to viral replication and mobilizing other immune system components. These findings indicate that IL-15 is a promising therapeutic agent for managing viral infections in farm animals, particularly when used in conjunction with modern vaccination strategies and biosecurity measures.

Directions for future research

The potent immunomodulatory properties of IL-15 make it a promising candidate for treating oncological diseases and viral infections. Modifying IL-15 or developing IL-15-based therapeutics is one of the most promising research directions. In the initial stage of developing IL-15-based therapeutics, recombinant human IL-15 (rhIL-15) was produced using recombinant DNA technology. This protein was expressed as a non-glycosylated monomer (molecular weight 13 kDa) in *Escherichia coli* [40]. Early clinical trials demonstrated that rhIL-15 modestly increased the number of NK cells and CD8+ T cells in patients with metastatic melanoma and metastatic renal cell carcinoma. However, the results highlighted some limitations, including the short half-life of rhIL-15 and the necessity for daily administration. Despite these limitations, rhIL-15 remains a potential therapeutic option for cancer and viral infections. Further studies are needed to address these limitations and provide more precise data on its safety and efficacy to enable its successful clinical application [22, 52].

Another promising approach for developing IL-15-based therapeutics involves modifying T cells expressing chimeric antigen receptors (CARs) with IL-15 genes. This strategy involves generating T cells capable of secreting proinflammatory cytokines, thereby enhancing their functionality and antitumor activity [53]. *In vitro* studies have shown that introducing IL-12 into CAR-T cells increases their antitumor efficacy. Similarly, IL-15 expression in CAR-T cells has demonstrated multiple advantages, including enhanced expansion, reduced cell death rates, decreased PD-1 receptor expression, and significantly improved antitumor effects in vivo compared with unmodified cells. However, the use of proinflammatory cytokines, such as IL-12 and IL-15, is associated with toxicity risks, which presents a challenge for clinical applications. Regulating cytokine secretion by limiting CAR binding to antigens is a promising approach to mitigating these risks. This strategy can reduce the adverse effects associated with the continuous expression of proinflammatory molecules. These findings indicate that equipping CAR-T cells with cytokine-secreting capabilities is a promising approach to improving their therapeutic efficacy. However, further studies are needed to assess the safety of this approach and to address its potential limitations before clinical implementation [54].

Currently, IL-15 combined with mAbs and bispecific antibodies is under investigation in several clinical trials [55, 56, 57]. rhIL-15 administration has been shown to significantly increase the number of activated NK cells. However, this increase alone is insufficient to achieve robust antitumor effects. Preclinical studies have shown that IL-15-based therapies enhance antibody-dependent cellular cytotoxicity (ADCC) and improve antitumor activity. For example, the combination of IL-15 and rituximab and alemtuzumab has demonstrated increased therapeutic efficacy in B-cell leukemia models. NK cells and macrophages play critical roles in this enhanced effect, contributing to elevated ADCC and improved therapeutic responses. Notably, ADCC has been reported to be further elevated in NK cells after their interaction with macrophages. These findings have provided the foundation for clinical trials investigating the use of IL-15 combined with humanized mAbs for treating acute leukemia, chronic lymphocytic leukemia, T cell lymphoma, and renal cell carcinoma [49].

Conclusion

IL-15 is a promising immunomodulator due to its ability to activate NK and T cells, thereby enhancing their antitumor and anti-infective activities. IL-15 administration stimulates the production of cytokines such as IFN-γ, which activate macrophages and increase their phagocytic activity, which is a critical component of the body's defense against pathogens. Despite its promise, the use of IL-15 in veterinary medicine requires further studies to establish optimal dosages and administration regimens because excessive immune activation can lead to inflammatory reactions and other side effects. IL-15 may become an integral part of combination therapies for infectious diseases in cattle, particularly in cases of pathogen resistance to conventional antibiotics. Thus, IL-15 is highly relevant in the context of combating antimicrobial resistance.

Contemporary research has been increasingly focused on exploring less studied ILs, investigating their roles in emerging pathophysiological processes, and developing drugs targeting their modulation. These advances open new avenues for personalized medicine. The significance of ILs cannot be overstated, as they are key regulators of numerous biological processes. A deeper understanding of their mechanisms can enable a more effective management of immune and inflammatory responses.

Authors' Contributions

KM and KT: developed the concept and design of the study, drafted the manuscript. ZA, DK and LT: conducted a comprehensive literature search, analyzed the collected data. MN and BA: performed final revision and proofreading of the manuscript. All authors have read, reviewed, and approved the final manuscript.

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