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Review Article

Internal Medicine Section

IL-21: The Future of Medicine

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ABSTRACT

Interleukin-21 (IL-21), a T- cell-derived cytokine, is a signaling molecule secreted by a subpopulation of T cells called follicular T helper (Tfh) cells. Studies have proved that IL-21 co-stimulates T cell proliferation by mediating enhanced T cell viability. This is done when IL-21 binds to its receptor, activating the phosphatidylinositol-3 kinase (PI-3K) signaling pathway and inducing B-cell Lymphoma-2 (Bcl-2) expression. Besides the B and T cells, IL-21 also regulates several Natural Killer (NK) cell functions. Due to its multi-faceted effects on different receptors, IL-21 has been used in multiple diseases. However, it was recently found that IL-21 had potent effect on various viruses including Lymphocytic Choriomeningitis Virus (LCMV), influenza virus and Vesicular Stomatitis Virus (VSV). The study proved that both B and CD4+ T cells need IL-21 signaling for generating long-term humoural immunity by generating long-lived plasma cells, thus, highlighting the importance of IL-21 in humoural immunity to viruses. These findings highlight how IL-21 could be important in the development of antiviral vaccines and vaccines for other potential life-threatening diseases leading scientists to design future vaccines to incorporate IL-21 directly or to use the ability to stimulate IL-21 as a gauge of vaccine activity. It is the need of the hour to go for larger studies which will be needed to better elucidate the cause and effect relationship and to demonstrate the effect size. It may possibly yield appreciable results in the future for untreatable diseases like HIV/AIDS.

Keywords: B-cells, CD4+, Humoural immunity, T-cells

INTRODUCTION

Interleukin-21 (IL-21) is a T-cell-derived cytokine which uses a heterodimeric receptor, composed of the common gamma-chain (CD132) and an IL-21Ralpha-chain [1]. IL-21 is a signaling molecule secreted by a subpopulation of T cells called follicular T helper (Tfh) cells. IL-21, a cytokine produced by various subsets of activated CD4+ T cells, regulates multiple innate and adaptive immune responses by controlling the proliferation and function of CD4+ and CD8+ T lymphocytes, driving the differentiation of Ig-secreting plasma cells and B cells into memory cells, enhancing the activity of Natural Killer (NK) cells and negatively regulating the differentiation and activity of regulatory T (Treg) cells. IL-21 can also stimulate non-immune cells to synthesise various inflammatory molecules [2]. In addition, IL-21 is involved in the formation of antibodies by exerting key functional controls over T and B cells.

Mode of Action

Studies have proved that IL-21 co-stimulates T cell proliferation by mediating enhanced T cell viability. This is done when IL-21 binds to its receptor, activating the phosphatidylinositol-3 kinase (PI-3K) signaling pathway and inducing Bcl-2 expression. Furthermore, it was proved that the activation of the PI-3K signaling pathway is essential for IL-21-mediated T cell survival [3]. Besides T-cells, it also stimulates B-cell proliferation as it can mediate apoptosis of B cells activated via Toll Like Receptor (TLR) signals [4,5]. On the contrary it induces B-cell proliferation in the presence of appropriate co-signals delivered by B-Cell Receptor (BCR) stimulation and CD40 ligand (L) expressed by T helper (Th) cells [6]. In addition, BLIMP-1 gene expression in vitro and in vivo has found to be actively involved in the differentiation of B lymphocytes into plasma cells [6].

Besides the B and T cells, IL-21 also regulates several NK cell functions. Soluble IL-21 co-stimulates IL-2 or IL-15 triggered NK cell expansion, hence, regulating its function [6]. In general the effects of IL-21 on immune regulation are multifaceted: it stimulates both innate and adaptive immunity, but on the other hand, it can also mediate negative regulatory effects on lymphoid and myeloid cells. These multifaceted responses, by activating some immune-regulatory pathways whereas inhibiting others, are important as they have strong implications both in autoimmunity and in cancer.

Efficacy in Clinical Studies

Due to its multi-faceted effects on different receptors, IL-21 has been used in multiple diseases. However, it was recently found that IL-21 had potent effect on various viruses including Lymphocytic Choriomeningitis Virus (LCMV), influenza virus and Vesicular Stomatitis Virus (VSV). The study proved that both B and CD4+ T cells need IL-21 signaling for generating long-term humoural immunity by generating long-lived plasma cells, thus, highlighting the importance of IL-21 in humoural immunity to viruses [7]. Owing to its increased capability and effectiveness against different viral diseases, it was also found that IL-21 was effective against Rheumatoid Arthritis (RA), indicating that it could be used for other autoimmune diseases in the future [8]. This was also proven in a recent data presented which supports that IL-21 and Tfh cells have a key role in the disease processes characterizing RA and Systemic Lupus Erythematosus (SLE) [9]. Similarly, in Giant Cell Arteritis (GCA), which is a granulomatous vasculitis of the aorta and its medium-sized branch vessels, IL-21 plays a significant role [9]. CD4+ T cells produce a broad spectrum of inflammatory cytokines (IL-17 and IL-21) which have a direct role in driving intimal hyperplasia and intramural neoangiogenesis [9]. The deficiency of the PD-1 immune checkpoint in GCA, promotes unopposed T-cell immunity. Excessive checkpoint activity is responsible for the underlying cancer immune evasion and is therapeutically targeted by immunotherapy with checkpoint inhibitors. Such checkpoint inhibitors, which unleash anti-cancer T-cells and induce immune-related toxicity, may lead to drug-induced vasculitis [10].

Besides the autoimmune diseases, IL-21 has been shown to play an important role in the CD8+ T cell response during acute and chronic viral infections. However, the role of IL-21 signaling in the CD4+ T cells response to viral infection remains incompletely

defined. Multiple models of vaccinia virus has shown intrinsic IL-21 signaling on CD4+ T cells, which was found to be critical for the formation of memory CD4+ T cells in vivo. It was further revealed that IL-21 promoted CD4 T cell survival in a mechanism dependent on activation of the STAT1 and STAT3 signaling pathways. In addition, the activation of Akt pathway was also required for IL-21 dependent survival of CD4+ T cells in vivo. These results identified a critical role for intrinsic IL-21 signaling in CD4+ T cells survival and memory formation in response to viral infection in vivo. This in turn may provide insights into the design of effective vaccine str ategies [11].

Besides the vaccine strategies, IL-21 exhibits essential roles in controlling chronic viral infections. This was seen in a cross-sectional study done on human T-cell lymphotropic virus type I (HTLV-1). HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a chronic progressive inflammatory disease of the nervous system. The main determinant of disease progression is efficiency of the Cytotoxic T-Lymphocyte (CTL) response to HTLV-1. The increase in IL-21 mRNA expression reflected the attempt of infected T cells to induce an appropriate antiviral response and the decrease in IL-21 protein expression reflected the inhibition of IL-21 mRNA translation by viral factors in favour of virus evasion and dissemination [12,13].

Future Prospects

These findings highlight how IL-21 could be important in the development of antiviral vaccines and vaccines for other potential life-threatening diseases leading scientists to use the ability of stimulating IL-21 to design future vaccines [12]. Signals from IL-21 appear to be necessary for generating long-lived plasma cells, which reside in the bone marrow and secrete antibodies. IL-21 may also be exploited as a therapeutic molecule to enhance immune functions in some cancers. Indeed, IL-21 has been shown to elicit antitumour immune responses in several preclinical tumour models. This antitumour, anticancer activity can be enhanced by combining IL-21 with other agents, which targets immune-regulatory circuits, tumour cells or other immune-enhancing molecules [14]. Furthermore, an improved understanding of the biological mechanisms of action involved in antibody-mediated complications after organ transplantation could lead to the development of novel therapeutic strategies, which could potentially prevent and treat graft-threatening antibody-mediated rejection [14]. In addition, potential molecular targets could restore mucosal barrier function and stimulate mucosal healing.

A phase I study of IL-21 combined with the anti-CTLA4 mAb Ipilimumab in unresectable stage III or stage IV melanoma was recently completed [15,16]. The purpose of this study was to determine the safety of this combination and achieve preliminary information on clinical benefits compared with Ipilimumab alone, but the results are not yet available [17]. Finally a safety study of IL-21 with the anti-PD-1 mAb Nivolumab in metastatic solid tumours is ongoing [16]. It is hoped that these and similar studies will show clinical benefit of IL-21 in combinational therapies for cancer [18].

CONCLUSION

Il-21, a T-cell derived cytokine, has the potential to be a possible life-saver in the future. Its multifaceted mode of action and efficacy seen in clinical trials could just be the right turning point for incurable viral diseases including Human Immunodeficiency Virus and Acquired Immune deficiency Syndrome (HIV/AIDS). In the near future, studies should focus on actual clinical end points in the diseased patients. This could lead scientists to use the ability of stimulating IL-21 to design future preventive vaccines and drugs. It is the need of the hour to go for larger studies which will be needed to better elucidate the cause and effect relationship and to demonstrate the effect size. It may possibly yield appreciable results in the future for untreatable diseases like HIV/AIDS.

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