IL-21 and Related Diseases

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Abstract

IL-21, which is produced by activated NKT cells and CD4+ T cells, exhibits pleiotropic effects not only on a variety of immune cells but also on non-immune cells. It has been demonstrated that IL-21 plays significant roles in the process of autoimmune diseases, inflammatory diseases and cancers. This review intends to give the reader an overview of this cytokine and the relationships between IL-21 and the related diseases of different body systems.

Keywords: IL-21; Autoimmune disease; Inflammatory disease; Cancer

Introduction

Interleukin-21 (IL-21), a four-α-helical-bundle type I cytokine, is mainly produced by CD4+ T cells and NKT cells and shows homology to IL-2, IL-4, IL-7, IL-9, and IL-15 [1]. Its receptor shares the common γ-chain (γc, or CD132) with the receptor complex of other five cytokines and binds to a unique IL-21Rα chain. IL-21R is expressed on immune cells, like T, B, natural killer (NK) cells, dendritic cells (DCs) and non-immune cells as well. IL-21 has pleiotropic effects on both innate and adaptive immune responses and plays crucial roles in the processes of autoimmune diseases, inflammatory diseases and cancers.

Biological Activity of IL-21 and IL-21 Receptor

IL-21 (IL-21) is a four-α-helical bundle type I cytokine with significant homology to IL-2, IL-4, IL-7, IL-9, and IL-15 [1]. The human IL-21 gene is mapped to 4q26-q27 and is closely linked to IL-2 gene, but not IL-15 gene which is at 4q31 [2]. In the mouse genome, IL-21 gene is located on chromosome 3, 95kb away from the IL-2 gene while the IL-15 gene is located on chromosome 8 [3]. It has been demonstrated that IL-21 is produced by activated NKT cells [4,5] and activated CD4+ T cells, including Th2 cells [6], Th17 cells [7,8], especially in follicular helper T (Tfh) cells [9,10] and exhibits pleiotropic effects not only on a variety of immune cells, like B cells, T cells, NK cells and DCs, but also on non-immune cells, such as fibroblasts, intestinal epithelial cells [1,4,11,12].

The IL-21 receptor (IL-21R) was discovered in 2000 [4,13]. As a novel class I cytokine receptor, IL-21R mediates its effects through the interaction with the common-gamma chain (γc), the family of which includes IL-2, IL-4, IL-7, IL-9, IL-13 and IL-15. The gene of this receptor is located on human chromosome 16p11, about 39kb away from the IL-4Rα gene. The murine IL-21R amino acid sequence is found to be 62% identical to the human sequence. The IL-21R gene in mouse lies 25kb from IL-4Rα gene on chromosome 7 and in the same transcriptional orientation [1-3]. The receptor can be detected in both resting and activated B cells, CD4+ and CD8+ T cell subsets, NK cells, DCs, and non-lymphoid tissues as well [3,4,13-17], indicating IL-21 has potent immunomodulatory functions in both innate and adaptive immune systems. Its biologic effect appears to depend on the various factors, such as the cell types, differentiation phase and activation status.

IL-21 signals via Janus-activated kinase/signal transducer and activator of transcription (JAK/STAT) signal transduction pathways. After binding of IL-21 to the IL-21Rα/γc complex, JAK1 and JAK3 are activated and then trigger the subsequent phosphorylation of STAT1 and STAT3 [13,18,19], and to a lesser extent, STAT4, STAT5 and STAT6 [13,20-22]. Additionally, the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways also involve in the IL-21 signaling transaction and are important for IL-21-mediated cell proliferation [21].

Hundreds of literatures published focus on the functions of IL-21 which include its amplification on Th17 population, its regulation of Th2 differentiation, its stimulation on B cell proliferation and antibody production, its induction of DCs maturation and NK cell activation, its promotion of matrix metalloproteinase (MMP) synthesis by fibroblasts and its increase of macrophage inflammatory protein (MIP)-3α production by intestinal epithelial cells. The diversity activities of IL-21 on different components suggest its participation in various diseases.

IL-21 in Skin Diseases

Psoriasis is a multifactorial, immune-mediated chronic skin disease [23,24]. IL-21 is over expressed in the skin of patients with psoriasis and stimulates the proliferation of human keratinocytes. Blockade of this cytokine may resolve inflammation by reducing the expressions of Th1 and Th17 genes and reducing keratinocyte proliferation [24,35]. When injected intradermally into human psoriasis-xenograft mice, IL-21 stimulated human keratinocytes to proliferate and causes epidermal hyperplasia [25].

The Smyth line (SL) of chicken is an animal model for human autoimmune vitiligo. Elevated leukocyte infiltration in early and active SLV accompanied by increased IL-21, IFN-γ, IL-10 expression was observed in SL vitiligo, which suggests IL-21 also involves in autoimmune vitiligo lesions [26].

Atopic dermatitis (AD) is an inflammatory skin disease with characteristics of eczematous lesions, drying and thickening of the skin, and severe itching [23]. Both IL-21 and IL-21R expressions were upregulated in skin lesions of AD patients [27,28]. With the administration of soluble IL-21R-IgG2aFc fusion protein, both IL21r−/− mice and WT mice failed to develop skin inflammation after epicutaneous allergic sensitization of tape-stripped skin [27].

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Melanoma is an aggressive and highly metastatic disease. Several phase I and II clinical trials have been performed to assess activity of IL-21 on melanoma [29-31]. Patients with no prior systemic therapy and with limited-disease metastatic melanoma (MM) were treated with IL-21. It had activity in the treatment of these patients with an overall response rate of 22.5% [31].

Therefore, IL-21 pathway is essential not only in inflammatory skin diseases, but also in skin cancer. Targeting this cytokine may be therapeutically effective in treating these diseases.

IL-21 in Hematological Diseases

As a pleiotropic cytokine, IL-21 exerts biologic effects in many types of hematological diseases, such as immune thrombocytopenia (ITP), chronic lymphocytic leukemia (CLL), multiple myeloma (MM) and lymphoma [32].

In patients with immune thrombocytopenia (ITP), plasma IL-21 level and IL-21+ T cells were significantly elevated compared to control individuals. The sources of IL-21 are CD3+CD8+ and CD3+CD8-T cells, the latter of which has positive correlations with Th17 and Th1 cells [33].

It has been demonstrated that IL-21 promotes the proliferation and pro-survival signals of myeloma and Hodgkin lymphoma (HL) cells [34-36]. IL-21 was detected in the bone marrow microenvironment of patients with Waldenstrom Macroglobulinemia (WM), a B-cell lymphoma characterized by elevated serum IgM and a lymphoplasmacytic bone marrow infiltration. It affects the proliferation and IgM secretion of WM tumor cells by inducing phosphorylation of STAT3 [37]. Scheeren et al. found that both IL-21R and IL-21 were expressed by HL cells. IL-21 can activate STAT3 and STAT5 in HL cell lines and activated human B cells [38]. In acute myeloid leukemia (AML) which is characterized by abnormal proliferation and development of myeloid cells and their precursors in blood and bone marrow, Th17 and its related cytokines, IL-23, transforming growth factor-beta (TGF-β), IL-1β, IL-6, IL-17, IL-22, and IL-21, might be involved in AML pathogenesis [39].

A combined therapy of rituximab, anti-CD20 antibodies, and weekly recombinant IL-21 was used to treat the patients with indolent B-cell malignancies and showed clinically active with durable complete remissions in a small subset of them [40]. Adoptive transfer of chimeric antigen receptor+ T cells cultured with IL-21 exhibited improved control of CD19+ B-cell malignancy in mice, suggesting that the IL-21 signal pathway has an effect on immunotherapy [41].

The blockade of IL-21 may be a reasonable therapeutic strategy for several hematological diseases.

IL-21 in Systemic Autoimmune and Rheumatic Diseases

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multi-organ inflammation. It is characterized by the production of pathogenic auto-antibodies and tissue injury as the results from the activation of autoreactive T and B cells [42]. In active SLE patients, increased IL-21 mRNA expression and intracellular IL-21 in peripheral blood CD4+ T cells as well as high concentration of plasma IL-21 was observed [43-45]. IL-21-producing CD4+ T cells were composed of CXCR5+ and CXCR5-CD4+ T cell subsets. Both of them were increased in SLE patients, the CXCR5-CD4+ subset correlating with increased Th17 and decreased Treg, while the CXCR5+CD4+ subset comprised mainly circulating Bcl6+CXCR5+CD4+ T cells that were correlated with increased circulating Bcl6+CXCR5+ germinal center B cells [44]. IL-21R expression decreased in peripheral blood B lymphocytes, which has a significant association with nephritis and high titer anti-double-strand DNA antibody [46]. With stimulation of IL-21, PBMCs increased the proportion of memory and plasma cells [43]. Furthermore, it has been reported that IL-21 and IL-21R polymorphisms are associated with SLE susceptibility [47,48]. IL-21 also plays a significant role in several mouse models of SLE. BXSB-Yaa mice develop an autoimmune syndrome similar to SLE. Compared with IL-21R-deficient mice, IL-21R-competent BXSB-Yaa mice developed severe SLE-related-symptoms, including hypergammaglobulinemia, autoantibody production, reduced frequencies of marginal zone B cells and monocytosis, renal disease, and premature morbidity [49]. When treated with soluble IL-21R-Fc for 24 weeks, BXSB-Yaa mice reduced the lymphocyte activation and improved kidney function [50,51]. MRL (lpr) mice lacking the icos gene had impaired extrafollicular differentiation of IgG (+) plasma cells accompanied by defects in IL-21 secretion and B cell helper function in CD4+ T cells [52]. The treatment of IL-21R-Fc fusion protein in the lupus-prone MRL-Fas (lpr) mouse model has reduced renal and skin lesion, the levels of circulating dsDNA autoantibodies and total sera IgG1 and IgG2a, and also lymphadenopathy [53]. These evidences suggest that IL-21 may represent a new therapeutic target for the treatment of SLE.

In rheumatoid arthritis (RA), a chronic inflammatory disease of polyarticular arthritis, elevated expressions at both mRNA and protein levels of IL-21 were detected by our group and were correlated with the presence of Th17 cells in synovial fluid (SF) and peripheral blood of the patients. IL-21, highly expressed by CCR6+CD4+ T cells, auto-regulated its own production in human CD4+ T cells and enhanced Th17 proliferation and suppresses Tregs, leading to the expression of RORC [54]. IL-21 production was strongly associated with the levels of auto-antibodies [55]. It was also reported that the proportion of Th17 cells, the mRNA expression of Bcl-6, a key transcription factor of Th17 cells, and plasma IL-21 concentrations in RA patients were increased [56]. Compared to active rheumatoid arthritis, remission RA patients showed decreased IL-21 level in sera, showing its pathogenesis role in RA [55,57]. Rheumatoid arthritis-like joint disease was developed spontaneously in IBP (IRF-4-binding protein) deficient mice in which the pathology was associated with an enhanced responsiveness of T cells to low levels of stimulation and with the inappropriate synthesis of IL-17 and IL-21 [58].

IL-21 in Neurological Disorders

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS), starting with increased migration of autoreactive lymphocytes across the blood-brain barrier [59]. Not only IL-21 but also IL-21R expressions were detected in acute and chronic active white matter MS lesions. Both of them were expressed by neurons in cortical areas [60]. In PBMCs, IL-21 mRNA expression was higher in MS-relapse patients than in either stable patients or healthy controls. Furthermore, serum IL-21 levels of patients with MS were found to be greater than controls. The high levels of IL-21 seen during relapses may be related to the role of this protein in promoting the proliferation of human CD4+ and CD8+ T cells [61,62]. In a Phase III trial of alemtuzumab treatment for MS, it was observed that patients with high baseline levels of serum IL-21 were at an increased risk of developing autoimmunity after therapy [63]. Experimental autoimmune encephalomyelitis (EAE) is an animal model for MS. When IL-21 was administrated before induction of EAE, it enhanced the inflammatory influx into the CNS as well as EAE severity by boosting NK cell function [64]. IL-21 potently induced Th17 differentiation and suppresses Foxp3 expression, which requires STAT3 and ROR-gamma.
IL-21 deficiency impaired the generation of Th17 cells and results in protection against EAE [7]. Analogously, IL-21R-deficient T cells were defective in generating a Th17 response [8] which were associated with several autoimmune diseases besides MS [65].

Neuromyelitis optica (NMO), known as Devic’s disease, is a disabling inflammatory condition that targets astrocytes in the optic nerves and spinal cord, producing a simultaneous or sequential optic neuritis and myelitis [66,67]. With PHA stimulation, PBMCs from NMO patients produced more IL-21 than healthy individuals. The release of IL-6 as well as IL-21 by polyclonal activated CD4+ T cells was directly correlated to neurological disability, which may be the reason for NMO patients’ being more refractory to corticoid treatment [68].

**IL-21 in Disorders of Gastrointestinal System**

Inflammatory bowel diseases (IBDs) are chronic intestinal disorders associated with aberrant activation of host immune responses toward components of the host luminal bacterial flora [69]. Two major clinically defined forms, Crohn’s disease (CD) and ulcerative colitis (UC), are chronic remittent or progressive inflammatory conditions that may affect the entire gastrointestinal tract and the colonic mucosa, respectively, and are associated with an increased risk for colon cancer [70,71]. IL-21 plays roles in the intestinal inflammation through effects on Th17 cells and the release of MMPs, which are involved in tissue remodeling [69,72]. Increased IL-21 production was detected in the patients with CD and UC [73,74]. The major source of IL-21 in active CD was produced by CD4+ and CD4+CD8+ intraepithelial lymphocytes (IELs) and lamina propria lymphocytes (LPLs) [75]. Blocking IL-21 significantly downregulated IL-17 production which is already known to be involved in IBD [76]. IL-21 also contributes to the ongoing Th1 mucosal response in CD [73,77]. It has been found that IL-21-producing cells co-expressed IFN-γ and to a lesser extent Th17 cytokines [75]. IL-21 also overexpressed in Helicobacter pylori (Hp)-infected gastric mucosa, promoted epithelial gelatinases synthesis and regulated MMPs production by enhancing NF-kappaB but not MAPK activation [78]. Inhibition of NF-kappaB pathway reduced IL-21-induced MMP-2 and MMP-9 production [78].

Recent genetic studies revealed that the polymorphisms within the IL2-IL21 linkage disequilibrium (LD) block show an association with IBD [79]. IL-21 and IL-2 are susceptibility genes in Han Chinese by haplotype-based analysis of ulcerative colitis risk loci [80].

Colonic IL-21 expression increased in the Gαi2-deficient mice which spontaneously developed severe colitis and colon cancer [81]. IL-21 was produced in excess in the gut of patients with UC-associated colon cancer [82]. This cytokine has a prominent function in tumor growth and immunosurveillance of colitis-associated tumorigenesis [83]. In mice with colitis-associated colon cancer (CAC) induced by azoxymethane (AOM) and dextran sulfate sodium (DSS), IL-21 was highly expressed in the intestines. But IL-21-deficient mice showed reduced mucosal damage and fewer tumour nodules after AOM+DSS induction. The activation of signal transducer and activator of transcription 3 (STAT3), a critical transcription factor for both Th17 and Th2 cells, increased in vivo and in vitro in colon tumour cells [84]. These findings indicate that the IL-21 concentrations may serve as a biomarker for monitoring HIV disease progression and the cytokine may be of great importance for vaccine design [99].

**IL-21 in HIV**

Human immunodeficiency virus (HIV) is a lentivirus that defects the quality and quantity of CD4+ T cells and causes acquired immunodeficiency syndrome (AIDS) [87]. Both CD4+ and CD8+ T cells were able to produce IL-21 in response to HIV-1 infection [88]. A longitudinal and cross-sectional study showed that the frequencies of IL-21-producing HIV-specific, Ag-experienced CD4+ T cells were decreased in HIV-infected viremic patients. Under IL-21 condition, CD4+ T cells from HIV-infected patients were prevented from spontaneous ex vivo death [89]. However, another study reported that HIV-infected individuals had greater circulating IL-21-producing CD4+ T cells in the blood compared with uninfected controls [90,91]. IL-21-producing CD4+ T cells likely contribute to viral containment by promoting CD8+ T cell activation and maintenance [90-93]. Meanwhile, HIV-1-specific IL-21-producing CD8+ T cells were also induced following primary infection and play a critical role in the maintenance of viremia control [88]. PBMCs from healthy donors were infected with HIV-1 in vitro, suppression of granulysin expression by CD8+ T cells and reduction of p-STAT3 and p-STAT5, following activation with IL-15 and IL-21, were detected. HIV-1 infection may reduce the antiviral microbicidal effect of activated CD8+ T cells by disrupting signaling events that are critical for the induction of granulysin [94]. IL-21 can enhance NK cell functions and survival in healthy and HIV-infected patients with minimal stimulation of viral replication [95]. The frequency of CXCR5+PD-1+ CD4+ T cells with IL-21 secretion and Bcl6 expression was found significantly high in lymph nodes of HIV-infected individuals. High levels of HIV viremia drive the expansion of Tfh cells, which leads to perturbations of B cell differentiation, resulting in dysregulated antibody production [96].

Similar to human HIV infection, during chronic simian immunodeficiency virus (SIV) infection of rhesus macaques (RM), IL-21-producing CD4+ T cells were significantly depleted in both blood and rectal mucosa, with the extent of this depletion correlating with the loss of Th17 cells that need IL-21 for their expansion. Furthermore, treatment with IL-21 augments cytotoxic potential of T cells and NK cells, increased in vivo Th17 cells, promoted B cell differentiation in SIV-infected RMs [97,98].

These findings indicate that the IL-21 concentrations may serve as a useful biomarker for monitoring HIV disease progression and the cytokine may be of great importance for vaccine design [99].

**Summary**

IL-21 plays pivotal roles in regulating immune systems. Besides the above diseases of various systems, IL-21 is reported to induce immunoglobulin production in B cells from patients with common variable immunodeficiency or selective IgA deficiency [100]. It involves class switching of immunoglobulin, thus playing an important role in occurrence of allergic disorders [101]. Additionally, IL-21 and IL-21R were increased in all transplanted organs to a similar extent and might promote graft-versus-host disease (GVHD) by enhancing the production of effector CD4+ T cells [102,103]. Recent studies revealed the potent pleiotropic effects of IL-21 in pulmonary disorders [104,105], renal diseases [106,107] and diabetes [108,109] as well. Although it is clear that IL-21 is important in the occurrence...
and development of many diseases, the details of its role in pathogenesis remain ambiguous, and further investigations are necessary to clarify its potential for therapeutic intervention. Moreover, treatment with recombinant IL-21 or targeting IL-21 strategy is already used in several clinical trials, but more clinical trials are needed to be done and more completed data are required to be analyzed and reported to fully evaluated the potential of this cytokine.

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