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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

Interleukin21 (IL-21), a four-α-helical-bundle type I cytokine, is mainly produced by $CD4^+$ T 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.

Biology of IL-21 and IL-21 Receptor

Interleukin-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 Treg 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 prosurvival 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$^+$ Tfh 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 Tfh cells, the mRNA expression of Bcl-6, a key transcription factor of Tfh 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 Tfh cells, in tumor and stromal cells was reduced in IL-21KO mice [84], while IFN-γ expression was increased, leading to increased tumour immune surveillance mediated by cytotoxic $CD8^+CD103^+$ T cells targeting E-cadherin(+) colonic tumour cells and therefore controlled the tumor growth [85]. Treated with neutralizing IL-21 antibody, the wild-type mice developed fewer smaller tumors than mice treated with a control antibody [82,84]. NFATc2-deficient mice significantly reduced tumor incidence due to the low levels of IL-21 and IL-6 secretion, leading to the reduction of endoscopic inflammation, increase of lamina propria T lymphocytes [86]. It demonstrates that NFAT transcription factors mediate T-cell activations and functions. The transcription factor NFATc2 plays a pivotal role in the development of colonic inflammation.

These observations indicate that IL-21 amplifies an inflammatory milieu that promotes CAC as well as IBD, and suggest that IL-21 may serve as a possible therapeutic target.

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 antimicrobial profile 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 $CXCR5^+PD\text{-}1^{hi}$ $CD4^+$ 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 (RMs), 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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References

1. Mehta DS, Wurster AL, Grusby MJ (2004) Biology of IL-21 and the IL-21 receptor. Immunol Rev 202: 84-95.
2. Parrish-Novak J, Foster DC, Holly RD, Clegg CH (2002) Interleukin-21 and the IL-21 receptor: novel effectors of NK and T cell responses. J Leukoc Biol 72: 856-863.
3. Collins M, Whitters MJ, Young DA (2003) IL-21 and IL-21 receptor: a new cytokine pathway modulates innate and adaptive immunity. Immunol Res 28: 131-140.
4. Parrish-Novak J, Dillon SR, Nelson A, Hammond A, Sprecher C, et al. (2000) Interleukin 21 and its receptor are involved in NK cell expansion and regulation of lymphocyte function. Nature 408: 57-63.
5. Coquet JM, Kyparissoudis K, Pellicci DG, Besra G, Berzins SP, et al. (2007) IL-21 is produced by NKT cells and modulates NKT cell activation and cytokine production. J Immunol 178: 2827-2834.
6. Wurster AL, Rodgers VL, Satoskar AR, Whitters MJ, Young DA, et al. (2002) Interleukin 21 is a T helper (Th) cell 2 cytokine that specifically inhibits the differentiation of naive Th cells into interferon gamma-producing Th1 cells. J Exp Med 196: 969-977.
7. Nurieva R, Yang XO, Martinez G, Zhang Y, Panopoulos AD, et al. (2007) Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. Nature 448: 480-483.
8. Korn T, Bettelli E, Gao W, Awasthi A, Jäger A, et al. (2007) IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. Nature 448: 484-487.
9. Vogelzang A, McGuire HM, Yu D, Sprent J, Mackay CR, et al. (2008) A fundamental role for interleukin-21 in the generation of T follicular helper cells. Immunity 29: 127-137.
10. Crotty S (2011) Follicular helper CD4 T cells (TFH). Annu Rev Immunol 29: 621-663.
11. Leonard WJ, Spolski R (2005) Interleukin-21: a modulator of lymphoid proliferation, apoptosis and differentiation. Nat Rev Immunol 5: 688-698.
12. Spolski R, Leonard WJ (2008) Interleukin-21: basic biology and implications for cancer and autoimmunity. Annu Rev Immunol 26: 57-79.
13. Ozaki K, Kikly K, Michalovich D, Young PR, Leonard WJ (2000) Cloning of a type I cytokine receptor most related to the IL-2 receptor beta chain. Proc Natl Acad Sci USA 97: 11439-11444.
14. Jin H, Carrio R, Yu A, Malek TR (2004) Distinct activation signals determine whether IL-21 induces B cell costimulation, growth arrest, or Bim-dependent apoptosis. J Immunol 173: 657-665.
15. Kasaian MT, Whitters MJ, Carter LL, Lowe LD, Jussif JM, et al. (2002) IL-21 limits NK cell responses and promotes antigen-specific T cell activation: a mediator of the transition from innate to adaptive immunity. Immunity 16: 559-569.
16. Brandt K, Bulfone-Paus S, Jenckel A, Foster DC, Paus R, et al. (2003) Interleukin-21 inhibits dendritic cell-mediated T cell activation and induction of contact hypersensitivity *in vivo*. J Invest Dermatol 121: 1379-1382.
17. Brandt K, Bulfone-Paus S, Foster DC, Rückert R (2003) Interleukin-21 inhibits dendritic cell activation and maturation. Blood 102: 4090-4098.
18. Habib T, Senadheera S, Weinberg K, Kaushansky K (2002) The common gamma chain (gamma c) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3. Biochemistry 41: 8725-8731.
19. Brandt K, Singh PB, Bulfone-Paus S, Rückert R (2007) Interleukin-21: a new modulator of immunity, infection, and cancer. Cytokine Growth Factor Rev 18: 223-232.
20. Strengell M, Matikainen S, Sirén J, Lehtonen A, Foster D, et al. (2003) IL-21 in synergy with IL-15 or IL-18 enhances IFN-gamma production in human NK and T cells. J Immunol 170: 5464-5469.
21. Zeng R, Spolski R, Casas E, Zhu W, Levy DE, et al. (2007) The molecular basis of IL-21-mediated proliferation. Blood 109: 4135-4142.
22. Asao H, Okuyama C, Kumaki S, Ishii N, Tsuchiya S, et al. (2001) Cutting edge: the common gamma-chain is an indispensable subunit of the IL-21 receptor complex. J Immunol 167: 1-5.
23. Costanzo A, Chimenti MS, Botti E, Caruso R, Sarra M, et al. (2010) IL-21 in the pathogenesis and treatment of skin diseases. J Dermatol Sci 60: 61-66.
24. Botti E, Spallone G, Caruso R, Monteleone G, Chimenti S, et al. (2012) Psoriasis, from pathogenesis to therapeutic strategies: IL-21 as a novel potential therapeutic target. Curr Pharm Biotechnol 13: 1861-1867.
25. Caruso R, Botti E, Sarra M, Esposito M, Stolfi C, et al. (2009) Involvement of interleukin-21 in the epidermal hyperplasia of psoriasis. Nat Med 15: 1013-1015.
26. Shi F, Erf GF (2012) IFN-γ, IL-21, and IL-10 co-expression in evolving autoimmune vitiligo lesions of Smyth line chickens. J Invest Dermatol 132: 642-649.
27. Jin H, Oyoshi MK, Le Y, Bianchi T, Koduru S, et al. (2009) IL-21R is essential for epicutaneous sensitization and allergic skin inflammation in humans and mice. J Clin Invest 119: 47-60.
28. Noh G, Lee J (2012) Atopic dermatitis and cytokines: the immunoregulatory and therapeutic implications of cytokines in atopic dermatitis--part II: negative regulation and cytokine therapy in atopic dermatitis. Recent Pat Inflamm Allergy Drug Discov 6: 248-261.
29. Rasmussen MA, Colding-Jørgensen M, Hansen LT, Bro R (2010) Multivariate evaluation of pharmacological responses in early clinical trials - a study of rIL-21 in the treatment of patients with metastatic melanoma. Br J Clin Pharmacol 69: 379-390.
30. Hashmi MH, Van Veldhuizen PJ (2010) Interleukin-21: updated review of Phase I and II clinical trials in metastatic renal cell carcinoma, metastatic melanoma and relapsed/refractory indolent non-Hodgkin's lymphoma. Expert Opin Biol Ther 10: 807-817.
31. Petrella TM, Tozer R, Belanger K, Savage KJ, Wong R, et al. (2012) Interleukin-21 has activity in patients with metastatic melanoma: a phase II study. J Clin Oncol 30: 3396-3401.
32. Ma J, Ma D, Ji C (2011) The role of IL-21 in hematological malignancies. Cytokine 56: 133-139.
33. Zhu X, Ma D, Zhang J, Peng J, Qu X, et al. (2010) Elevated interleukin-21 correlated to Th17 and Th1 cells in patients with immune thrombocytopenia. J Clin Immunol 30: 253-259.
34. Brenne AT, Ro TB, Waage A, Sundan A, Borset M, et al. (2002) Interleukin-21 is a growth and survival factor for human myeloma cells. Blood 99: 3756-3762.
35. Ménoret E, Maïga S, Descamps G, Pellat-Deceunynck C, Fraslon C, et al. (2008) IL-21 stimulates human myeloma cell growth through an autocrine IGF-1 loop. J Immunol 181: 6837-6842.
36. Dien Bard J, Gelebart P, Anand M, Zak Z, Hegazy SA, et al. (2009) IL-21 contributes to JAK3/STAT3 activation and promotes cell growth in ALK-positive anaplastic large cell lymphoma. Am J Pathol 175: 825-834.
37. Hodge LS, Ziesmer SC, Yang ZZ, Secreto FJ, Gertz MA, et al. (2012) IL-21 in the bone marrow microenvironment contributes to IgM secretion and proliferation of malignant cells in Waldenstrom macroglobulinemia. Blood 120: 3774-3782.
38. Scheeren FA, Diehl SA, Smit LA, Beaumont T, Naspetti M, et al. (2008) IL-21 is expressed in Hodgkin lymphoma and activates STAT5: evidence that activated STAT5 is required for Hodgkin lymphomagenesis. Blood 111: 4706-4715.
39. Li P, Ji M, Park J, Bunting KD, Ji C, et al. (2012) Th17 related cytokines in acute myeloid leukemia. Front Biosci 17: 2284-2294.
40. Timmerman JM, Byrd JC, Andorsky DJ, Yamada RE, Kramer J, et al. (2012) A phase I dose-finding trial of recombinant interleukin-21 and rituximab in

relapsed and refractory low grade B-cell lymphoproliferative disorders. Clin Cancer Res 18: 5752-5760.

41. Singh H, Figliola MJ, Dawson MJ, Huls H, Olivares S, et al. (2011) Reprogramming CD19-specific T cells with IL-21 signaling can improve adoptive immunotherapy of B-lineage malignancies. Cancer Res 71: 3516-3527.

42. Choi J, Kim ST, Craft J (2012) The pathogenesis of systemic lupus erythematosus-an update. Curr Opin Immunol 24: 651-657.

43. Nakou M, Papadimitraki ED, Fanouriakis A, Bertsias GK, Choulaki C, et al. (2012) Interleukin-21 is increased in active systemic lupus erythematosus patients and contributes to generation of plasma B cells. Clin Exp Rheumatol .

44. Terrier B, Costedoat-Chalumeau N, Garrido M, Geri G, Rosenzwajg M, et al. (2012) Interleukin 21 correlates with T cell and B cell subset alterations in systemic lupus erythematosus. J Rheumatol 39: 1819-1828.

45. Wong CK, Wong PT, Tam LS, Li EK, Chen DP, et al. (2010) Elevated production of B cell chemokine CXCL13 is correlated with systemic lupus erythematosus disease activity. J Clin Immunol 30: 45-52.

46. Mitoma H, Horiuchi T, Kimoto Y, Tsukamoto H, Uchino A, et al. (2005) Decreased expression of interleukin-21 receptor on peripheral B lymphocytes in systemic lupus erythematosus. Int J Mol Med 16: 609-615.

47. Sawalha AH, Kaufman KM, Kelly JA, Adler AJ, Aberle T, et al. (2008) Genetic association of interleukin-21 polymorphisms with systemic lupus erythematosus. Ann Rheum Dis 67: 458-461.

48. Webb R, Merrill JT, Kelly JA, Sestak A, Kaufman KM, et al. (2009) A polymorphism within IL21R confers risk for systemic lupus erythematosus. Arthritis Rheum 60: 2402-2407.

49. Bubier JA, Sproule TJ, Foreman O, Spolski R, Shaffer DJ, et al. (2009) A critical role for IL-21 receptor signaling in the pathogenesis of systemic lupus erythematosus in BXSB-Yaa mice. Proc Natl Acad Sci USA 106: 1518-1523.

50. Bubier JA, Bennett SM, Sproule TJ, Lyons BL, Olland S, et al. (2007) Treatment of BXSB-Yaa mice with IL-21R-Fc fusion protein minimally attenuates systemic lupus erythematosus. Ann N Y Acad Sci 1110: 590-601.

51. Li J, Pan HF, Cen H, Tian J, Ma Y, et al. (2011) Interleukin-21 as a potential therapeutic target for systemic lupus erythematosus. Mol Biol Rep 38: 4077-4081.

52. Odegard JM, Marks BR, DiPlacido LD, Poholek AC, Kono DH, et al. (2008) ICOS-dependent extrafollicular helper T cells elicit IgG production via IL-21 in systemic autoimmunity. J Exp Med 205: 2873-2886.

53. Herber D, Brown TP, Liang S, Young DA, Collins M, et al. (2007) IL-21 has a pathogenic role in a lupus-prone mouse model and its blockade with IL-21R.Fc reduces disease progression. J Immunol 178: 3822-3830.

54. Niu X, He D, Zhang X, Yue T, Li N, et al. (2010) IL-21 regulates Th17 cells in rheumatoid arthritis. Hum Immunol 71: 334-341.

55. Zivojinovic S, Pejnovic N, Sefik-Bukilica M, Kovacevic L, Soldatovic I, et al. (2012) Effects of TNF inhibitor on innate inflammatory and Th17 cytokines in stimulated whole blood from rheumatoid arthritis patients. Inflammopharmacology 20: 323-330.

56. Ma J, Zhu C, Ma B, Tian J, Baidoo SE, et al. (2012) Increased frequency of circulating follicular helper T cells in patients with rheumatoid arthritis. Clin Dev Immunol 2012: 827480.

57. Niu X, He D, Deng S, Li W, Xi Y, et al. (2011) Regulatory immune responses induced by IL-1 receptor antagonist in rheumatoid arthritis. Mol Immunol 49: 290-296.

58. Chen Q, Yang W, Gupta S, Biswas P, Smith P, et al. (2008) IRF-4-binding protein inhibits interleukin-17 and interleukin-21 production by controlling the activity of IRF-4 transcription factor. Immunity 29: 899-911.

59. Compston A, Coles A (2008) Multiple sclerosis. Lancet 372: 1502-1517.

60. Tzartos JS, Craner MJ, Friese MA, Jakobsen KB, Newcombe J, et al. (2011) IL-21 and IL-21 receptor expression in lymphocytes and neurons in multiple sclerosis brain. Am J Pathol 178: 794-802.

61. Tegla CA, Cudrici CD, Azimzadeh P, Singh AK, Trippe R 3rd, et al. (2013) Dual role of Response gene to complement-32 in multiple sclerosis. Exp Mol Pathol 94: 17-28.

62. Jones JL, Phuah CL, Cox AL, Thompson SA, Ban M, et al. (2009) IL-21 drives secondary autoimmunity in patients with multiple sclerosis, following therapeutic lymphocyte depletion with alemtuzumab (Campath-1H). J Clin Invest 119: 2052-2061.

63. Costelloe L, Jones J, Coles A (2012) Secondary autoimmune diseases following alemtuzumab therapy for multiple sclerosis. Expert Rev Neurother 12: 335-341.

64. Vollmer TL, Liu R, Price M, Rhodes S, La Cava A, et al. (2005) Differential effects of IL-21 during initiation and progression of autoimmunity against neuroantigen. J Immunol 174: 2696-2701.

65. Waite JC, Skokos D (2012) Th17 response and inflammatory autoimmune diseases. Int J Inflam 2012: 819467.

66. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG (2007) The spectrum of neuromyelitis optica. Lancet Neurol 6: 805-815.

67. Morrow MJ, Wingerchuk D (2012) Neuromyelitis optica. J Neuroophthalmol 32: 154-166.

68. Linhares UC, Schiavoni PB, Barros PO, Kasahara TM, Teixeira B, et al. (2012) The *Ex vivo* Production of IL-6 and IL-21 by CD4(+) T Cells is Directly Associated with Neurological Disability in Neuromyelitis Optica Patients. J Clin Immunol.

69. Maloy KJ, Powrie F (2011) Intestinal homeostasis and its breakdown in inflammatory bowel disease. Nature 474: 298-306.

70. Kaser A, Zeissig S, Blumberg RS (2010) Inflammatory bowel disease. Annu Rev Immunol 28: 573-621.

71. Abraham C, Cho JH (2009) Inflammatory bowel disease. N Engl J Med 361: 2066-2078.

72. Maloy KJ, Kullberg MC (2008) IL-23 and Th17 cytokines in intestinal homeostasis. Mucosal Immunol 1: 339-349.

73. Monteleone G, Monteleone I, Fina D, Vavassori P, Del Vecchio Blanco G, et al. (2005) Interleukin-21 enhances T-helper cell type I signaling and interferon-gamma production in Crohn's disease. Gastroenterology 128: 687-694.

74. Sarra M, Monteleone I, Stolfi C, Fantini MC, Sileri P, et al. (2010) Interferon-gamma-expressing cells are a major source of interleukin-21 in inflammatory bowel diseases. Inflamm Bowel Dis 16: 1332-1339.

75. Sarra M, Cupi ML, Monteleone I, Franzè E, Ronchetti G, et al. (2012) IL-15 positively regulates IL-21 production in celiac disease mucosa. Mucosal Immunol.

76. Rovedatti L, Kudo T, Biancheri P, Sarra M, Knowles CH, et al. (2009) Differential regulation of interleukin 17 and interferon gamma production in inflammatory bowel disease. Gut 58: 1629-1636.

77. Fina D, Sarra M, Caruso R, Del Vecchio Blanco G, Pallone F, et al. (2008) Interleukin 21 contributes to the mucosal T helper cell type 1 response in coeliac disease. Gut 57: 887-892.

78. Caruso R, Fina D, Peluso I, Fantini MC, Tosti C, et al. (2007) IL-21 is highly produced in Helicobacter pylori-infected gastric mucosa and promotes gelatinases synthesis. J Immunol 178: 5957-5965.

79. Márquez A, Orozco G, Martínez A, Palomino-Morales R, Fernández-Arquero M, et al. (2009) Novel association of the interleukin 2-interleukin 21 region with inflammatory bowel disease. Am J Gastroenterol 104: 1968-1975.

80. Shi J, Zhou L, Zhernakova A, Qian J, Zhu F, et al. (2011) Haplotype-based analysis of ulcerative colitis risk loci identifies both IL2 and IL21 as susceptibility genes in Han Chinese. Inflamm Bowel Dis 17: 2472-2479.

81. Götlind YY, Fritsch Fredin M, Kumawat AK, Strid H, Willén R, et al. (2013) Interplay between Th1 and Th17 effector T-cell pathways in the pathogenesis of spontaneous colitis and colon cancer in the Gαi2-deficient mouse. Int Immunol 25: 35-44.

82. Stolfi C, Rizzo A, Franzè E, Rotondi A, Fantini MC, et al. (2011) Involvement of interleukin-21 in the regulation of colitis-associated colon cancer. J Exp Med 208: 2279-2290.

83. Kesselring R, Jauch D, Fichtner-Feigl S (2012) Interleukin 21 impairs tumor immunosurveillance of colitis-associated colorectal cancer. Oncoimmunology 1: 537-538.

84. Jauch D, Martin M, Schiechl G, Kesselring R, Schlitt HJ, et al. (2011) Interleukin

21 controls tumour growth and tumour immunosurveillance in colitis-associated tumorigenesis in mice. Gut 60: 1678-1686.

85. Stolfi C, Pallone F, Macdonald TT, Monteleone G (2012) Interleukin-21 in cancer immunotherapy: Friend or foe? Oncoimmunology 1: 351-354.

86. Gerlach K, Daniel C, Lehr HA, Nikolaev A, Gerlach T, et al. (2012) Transcription factor NFATc2 controls the emergence of colon cancer associated with IL-6-dependent colitis. Cancer Res 72: 4340-4350.

87. Pallikkuth S, Parmigiani A, Pahwa S (2012) The role of interleukin-21 in HIV infection. Cytokine Growth Factor Rev 23: 173-180.

88. Williams LD, Bansal A, Sabbaj S, Heath SL, Song W, et al. (2011) Interleukin-21-producing HIV-1-specific CD8 T cells are preferentially seen in elite controllers. J Virol 85: 2316-2324.

89. Iannello A, Boulassel MR, Samarani S, Debbeche O, Tremblay C, et al. (2010) Dynamics and consequences of IL-21 production in HIV-infected individuals: a longitudinal and cross-sectional study. J Immunol 184: 114-126.

90. Yue FY, Lo C, Sakhdari A, Lee EY, Kovacs CM, et al. (2010) HIV-specific IL-21 producing $CD4^+$ T cells are induced in acute and chronic progressive HIV infection and are associated with relative viral control. J Immunol 185: 498-506.

91. Singh A, Vajpayee M, Ali SA, Mojumdar K, Chauhan NK, et al. (2012) HIV-1 diseases progression associated with loss of Th17 cells in subtype 'C' infection. Cytokine 60: 55-63.

92. Parmigiani A, Pallin MF, Schmidtmayerova H, Lichtenheld MG, Pahwa S (2011) Interleukin-21 and cellular activation concurrently induce potent cytotoxic function and promote antiviral activity in human CD8 T cells. Hum Immunol 72: 115-123.

93. Chevalier MF, Jülg B, Pyo A, Flanders M, Ranasinghe S, et al. (2011) HIV-1-specific interleukin-21+ $CD4^+$ T cell responses contribute to durable viral control through the modulation of HIV-specific $CD8^+$T cell function. J Virol 85: 733-741.

94. Hogg AE, Bowick GC, Herzog NK, Cloyd MW, Endsley JJ (2009) Induction of granulysin in $CD8^+$T cells by IL-21 and IL-15 is suppressed by human immunodeficiency virus-1. J Leukoc Biol 86: 1191-1203.

95. Iannello A, Boulassel MR, Samarani S, Tremblay C, Toma E, et al. (2010) IL-21 enhances NK cell functions and survival in healthy and HIV-infected patients with minimal stimulation of viral replication. Leukoc Biol 87: 857-867.

96. Lindqvist M, van Lunzen J, Soghoian DZ, Kuhl BD, Ranasinghe S, et al. (2012) Expansion of HIV-specific T follicular helper cells in chronic HIV infection. J Clin Invest 122: 3271-3280.

97. Micci L, Cervasi B, Ende ZS, Iriele RI, Reyes-Aviles E, et al. (2012) Paucity of IL-21-producing CD4(+) T cells is associated with Th17 cell depletion in SIV infection of rhesus macaques. Blood 120: 3925-3935.

98. Pallikkuth S, Rogers K, Villinger F, Dosterii M, Vaccari M, et al. (2011) Interleukin-21 administration to rhesus macaques chronically infected with simian immunodeficiency virus increases cytotoxic effector molecules in T cells and NK cells and enhances B cell function without increasing immune activation or viral replication. Vaccine 29: 9229-9238.

99. Pallikkuth S, Parmigiani A, Pahwa S (2012) The role of interleukin-21 in HIV infection. Cytokine Growth Factor Rev 23: 173-180.

100. Borte S, Pan-Hammarström Q, Liu C, Sack U, Borte M, et al. (2009) Interleukin-21 restores immunoglobulin production *ex vivo* in patients with common variable immunodeficiency and selective IgA deficiency. Blood 114: 4089-4098.

101. Kemeny DM (2012) The role of the T follicular helper cells in allergic disease. Cell Mol Immunol 9: 386-389.

102. Kobayashi S, Haruo N, Sugane K, Ochs HD, Agematsu K (2009) Interleukin-21 stimulates B-cell immunoglobulin E synthesis in human beings concomitantly with activation-induced cytidine deaminase expression and differentiation into plasma cells. Hum Immunol 70: 35-40.

103. Oh I, Ozaki K, Meguro A, Hatanaka K, Kadowaki M, et al. (2010) Altered effector $CD4^+$ T cell function in IL-21R-/- $CD4^+$ T cell-mediated graft-versus-host disease. J Immunol 185: 1920-1926.

104. Yerkovich ST, Hales BJ, Carroll ML, Burel JG, Towers MA, et al. (2012) Reduced rhinovirus-specific antibodies are associated with acute exacerbations of chronic obstructive pulmonary disease requiring hospitalisation. BMC Pulm Med 12: 37.

105. Boyden AW, Legge KL, Waldschmidt TJ (2012) Pulmonary infection with influenza A virus induces site-specific germinal center and T follicular helper cell responses. PLoS One 7: e40733.

106. Turner JE, Paust HJ, Steinmetz OM, Panzer U (2010) The Th17 immune response in renal inflammation. Kidney Int 77: 1070-1075.

107. Grünwald V, Desar IM, Haanen J, Fiedler W, Mouritzen U, et al. (2011) A phase I study of recombinant human interleukin-21 (rIL-21) in combination with sunitinib in patients with metastatic renal cell carcinoma (RCC). Acta Oncol 50: 121-126.

108. Mariño E, Tan B, Binge L, Mackay CR, Grey ST (2012) B-cell cross-presentation of autologous antigen precipitates diabetes. Diabetes 61: 2893-2905.

109. Liu SM, Lee DH, Sullivan JM, Chung D, Jäger A, et al. (2011) Differential IL-21 signaling in APCs leads to disparate Th17 differentiation in diabetes-susceptible NOD and diabetes-resistant NOD.Idd3 mice. J Clin Invest 121: 4303-4310.

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