Journal of
Clinical & Cellular Immunology

Jung and Guay, J Clin Cell Immunol 2011, S1
DOI: 10.4172/2155-9899.S1-002

Review Article Open Access

Role of IL-21 in Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus is a chronic autoimmune disease that affects multiple organ systems and tissues. Activation and differentiation of autoreactive T and B cells, and the formation of pathogenic autoantibodies are central to disease pathogenesis. IL-21 is the most recently identified member of the family of cytokines whose receptors share the common γ_c. IL-21 is a pleotropic cytokine that regulates the activation, differentiation and expansion of B and T cells. Here, we review the role of IL-21 in T and B cell biology, and provide insight into the potential role of IL-21 in the development of SLE.

Keywords: Systemic Lupus Erythematosus; Interleukin-21

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that targets multiple organ systems and tissues, including the kidneys, skin, joints, hearts, lung and central nervous system. It has been estimated that there are approximately 1.5 million people in the United States and over 5 million people worldwide affected by the disease. The etiology of SLE is unknown, but genetic and environmental factors are thought to play a role. The underlying immune mechanisms driving SLE are also poorly understood, but it is widely accepted that the activation of autoreactive B cells and the subsequent production of autoantibodies are central to disease pathogenesis [1]. The modest improvement following treatment with belimumab, a B cell targeted therapy, in signs and symptoms of serologically active lupus patients, demonstrates a potential role for B cells in the pathogenesis of SLE [2]. However, these results in the clinic also suggest that non-B cell mediated processes may also play a role in the development of the disease. There is mounting evidence that T cells may contribute to the inflammatory processes involved in SLE through the action of T follicular helper cells and Th17 cells [3,4]. Thus, pathways that regulate the activity of both B and T cells may be critical mediators of disease in SLE.

IL-21 is the most recently discovered member of the type I family of cytokines whose receptor shares a common γ chain (γ_c) with the receptors for IL-2, IL-4, IL-7, IL-9, and IL-15 [5,6]. IL-21 has a four helix structure, which is most similar to IL-2, IL-4 and IL-15. The receptor for IL-21, IL-21R, is comprised of a heterodimeric complex of IL-21Rα paired with γ_c. Binding of IL-21 to IL-21R results in the activation of Jak1, Jak2, STAT3 and to a lesser extent STAT1 and STAT5 [7-9]. IL-21R is expressed on most immune cells, including B cells, CD4+ T cells, CD8+ T cells, NK cells, NKT cells, monocytes and dendritic cells and also on some non-hematopoeitic cells, suggesting broad effects on many cell types and tissues within the body [5,7,10-15]. Since its discovery, it has become evident that IL-21 is essential for regulating multiple facets of B and T cell biology, and may therefore be important for the inflammatory responses that drive pathogenesis in many autoimmune diseases. Here, we review the effects of IL-21 on B and T cell responses, and provide insight into the contribution of the IL-21 pathway to the pathogenesis of SLE.

Genetic association of IL-21 Pathway with SLE

Genome wide association studies have identified a number of loci associated with increased risk for the development of autoimmunity. Particularly, polymorphisms within the IL-2/IL-21 region of chromosome 4 are associated with heightened risk of developing SLE. Two independent studies have identified three polymorphisms within the IL-21 gene within patients of European, Hispanic and African American decent, and two of these polymorphisms are associated with increased risk of developing SLE [16,17]. Another study also genotyped 17 SNPs in the IL-21R gene, and identified a single polymorphism within the IL-21R gene that is significantly associated with SLE [18]. The functional consequences of these polymorphisms on IL-21 and IL-21R expression and function have not yet been examined. Interestingly, all three polymorphisms associated with lupus are located within the intronal region of their respective genes.

Production of IL-21

Initial expression studies in healthy individuals demonstrated that IL-21 is produced by peripheral CD3+ T cells. It is now appreciated that IL-21 is produced by NKT cells and a spectrum of activated CD4+ T cells [5]. IL-21 is produced by T follicular helper (TFH) cells, a specialized subset of T cells that promote B cell memory formation and differentiation to class switched plasma cells [19-21]. CD4+ extrafollicular helper cells, a unique population of T cells that promote autoantibody responses at extrafollicular sites in the secondary lymphoid tissues of some animal models of lupus, have also been shown to produce IL-21 [22]. Th1, Th2, and Th17 cells can also be induced to secrete IL-21 under certain circumstances *in vitro* [23-27]. IL-21 producing Th2 and Th17 cells have also been identified in the peripheral blood of some autoimmune patients [28]. IL-21 is markedly elevated in the plasma of patients with active SLE, and IL-21 mRNA is also over expressed in lesional tissue of cutaneous lupus patients when compared to skin from normal healthy controls [29,30]. The exact source of IL-21 in lupus patients is not known. Notably, TFH and Th17 cells are elevated in the peripheral blood of SLE patients, and positively correlate with disease activity [31,32]. Th17 cells have also been identified in lesional skin and kidney tissue from SLE patients

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Received June 15, 2011; **Accepted** September 10, 2011; **Published** September 13, 2011

Citation: Jung SS, Guay HM (2011) Role of IL-21 in Systemic Lupus Erythematosus. J Clin Cell Immunol S1:002. doi:10.4172/2155-9899.S1-002

[31,33,34]. Thus, current data suggest that TFH and Th17 cells may be the major producers of IL-21 in SLE patients, although this remains to be formally shown.

Regulation of B cell responses

XSCID is a severe immunodeficient state that results from a mutation in the common γ_c [6,35]. Loss of both IL-21 and IL-4 receptor-mediated signaling account for the B cell defects observed in human XSCID, indicating a critical role for IL-21 in normal B cell function [36]. Studies with both mouse and human cells have demonstrated that IL-21 is clearly involved in the development, activation, differentiation and death of B cells. Although IL-21 deficient mice have an apparently normal mature B cell repertoire, recent studies have demonstrated that IL-21 accelerates B cell maturation at early stages of development in the bone marrow [37]. *In vitro* studies have also shown that IL-21 differentially regulates B cell activation and apoptosis depending on the costimulatory signals provided to B cells. IL-21 enhances B cell activation and proliferation, and induces differentiation to IgG-secreting plasma cells when stimulated in combination with anti-IgM and anti-CD40 [38,39]. Accordingly, under these culture conditions IL-21 induces the expression of AID, Blimp-1, XBP-1, and IRF-4, factors involved in class switch recombination and plasma cell differentiation. Notably, AID is also involved in somatic hypermutation of Ig variable region genes; however, stimulation of B cells with IL-21 in combination with anti-IgM and anti-CD40 was not sufficient to induce somatic hypermutation. Interestingly, IL-21 negatively regulates class switch recombination (CSR) to IgE in mice through the induction of Id2; however, this does not appear to be the case for human B cells [40,41]. Thus, IL-21 is a potent inducer of class switch recombination and plasma cell differentiation [39,42,43]. In contrast, IL-21 induces apoptosis of naïve B cells when stimulated with either anti-CD40 or TLR agonists (ie, CpG and LPS) in the absence of BCR signals [15,39,44,45]. Although the significance of IL-21 induced B cell apoptosis *in vivo* is not understood, this may represent a potential mechanism by which IL-21 prevents the activation of autoreactive B cells in healthy individuals.

Regulation of antibody pesponses

B cells face a number of cell fate decisions during the development of antibody responses. Following activation, a subset of B cells rapidly differentiate into short-lived plasma cells to generate a burst of low affinity antibodies shortly after insult [46]. Another subset of B cells form germinal centers (GC) with T follicular helper cells and dendritic cells, in which they undergo a dynamic process to mature into high affinity class switched memory B cells and terminally differentiated long-lived plasma cells [47,48]. Over-expression of IL-21 resulted in spontaneous hypergammaglobulinemia and autoantibody production in mice [36]. IL-21 also induces CSR and plasma cell differentiation *in vitro*, suggesting a regulatory role for IL-21 in the development of isotype switched antibody responses [39,42,49]. Indeed, IL-21R KO mice have reduced antigen-specific IgG antibody responses 7-10 days following immunization with numerous T cell-dependent (TD) antigens [36]. However, IL-21R KO mice have been reported to generate normal IgG antibody responses to *Salmonella*, which elicits a completely extrafollicular antibody response, and long-term IgG antibody responses to some TD antigens, indicating that the requirement for IL-21 for isotype switching and plasma cell differentiation to foreign antigens is not absolute [50-52].

IL-21 is an important autocrine growth factor for TFH cells, and IL-21 can impact the development and maintenance of these cells [20,50,53]. IL-21 has also been reported to directly drive the differentiation of TFH and GC B cells through the induction of the transcription factor Bcl-6 [50,52]. However, the requirement for IL-21 in TFH and GC B cell development appears to be dependent on the time points examined and the immunogens used [51,52,54,55]. Studies using virus-like particles demonstrated that stimulation of B cells by TLR ligands may overcome the need for IL-21 mediated signals in GC formation [55]. Whether TLR mediated signals can fully compensate for IL-21 driven GC maintenance or memory B cells and plasma cell formation was not examined. IL-21R KO mice also formed TFH cells, GC B cells, and isotype switched memory cells and long-lived plasma cells in response to several TD antigens, although IL-21 was important for affinity maturation and reactivation of memory cells [51,52]. Memory B cells are also reduced in the peripheral blood of STAT3 deficient humans, and naïve B cells from these individuals fail to differentiate into plasma cells following stimulation with IL-21 *in vitro*, providing further evidence that IL-21 may be critical for establishing long-term humoral immunity in humans [56]. Collectively, these studies have shown that IL-21 can influence each stage of an antibody response, however its role depends upon the contextual cues provided to the B cell (ie. strength of BCR mediated signaling, adjuvant, quality of T cell help, etc.). IL-21 influences isotype switching, germinal center responses, and differentiation of plasma cells and memory B cells, and is critical for the normal development of antibody responses. Thus, IL-21 may play a significant role in the initiation and maturation of autoreactive B cell responses in SLE.

Lupus patients are characterized by high titers of isotype switched autoantibodies [1]. These individuals also often have elevated numbers of plasmablasts, pre-GC B cells and TFH cells in the blood [4,57-59]. Together, these data suggest that lupus patients have increased B cell and GC activity. IL-21 may account for these abnormalities in lupus patients in two ways. First, IL-21 may act on B cells themselves to support B cell expansion, autoantibody production, isotype switching and maturation to memory B cells and plasma cells within GC. Additionally, IL-21 may induce the expansion of the TFH population within SLE patients, further potentiating activation and maturation of autoreactive B cells in these patients.

Enhancement of T cell differentiation, proliferation and effector function

IL-21 is an important regulator of T cell expansion, differentiation and effector function [60,61]. In mouse and humans, IL-21 enhances anti-CD3 induced proliferation of T cells, and can act in concert with other type I cytokines to further enhance the growth of CD4 T cells. IL-21 can synergize with IL-15 to promote Th1 differentiation of human T cells by enhancing the expression of the transcription factor T-bet and activation of STAT4 [62]. IL-21 also regulates human CD8 T cell activation, survival, memory formation and recall responses [63]. IL-21 can further synergize with IL-7 and IL-15 to enhance the growth and cytotoxic effector functions of CD8 T cells [64-66]. The role of Th1 and CD8 T cells in SLE is not well understood, although Th1 and CD8 derived cytokines, such as IFN-γ, may contribute to disease pathology.

In addition to serving as a growth factor for TFH cells, IL-21 is also important for the expansion and maintenance of the Th17 lineage [27,53,60,67]. Th17 cells produce an array of proinflammatory molecules including IL-1, IL-6, IL-17, IL-21, IL-22, and TNFα [68]. Several lines of evidence link Th17 cells, and their prototype cytokine, IL-17, to pathology in SLE. IL-17 and Th17 cells are elevated in the peripheral blood of SLE patients, and correlate with disease activity in

these patients [31,32]. IL-17 is also detectable in the affected skin and kidneys of cutaneous lupus patients [31,33,34]. Further, evidence from the BXD2 and MRL-Fas^{lpr} animal models of lupus also demonstrate that Th17 cells and IL-17 may be key mediators of disease pathology in SLE [69-71]. The exact mechanism by which IL-17 contributes to disease in the MRL-Fas^{lpr} mice is not known. In BXD2 mice, IL-17 drives the autoreactive germinal center response and subsequently autoantibody formation. In humans, IL-17 has been shown to synergize with BLyS to enhance the survival and expansion of B cells, as well as induce isotype switching and differentiation to plasma cells [72]. In addition, IL-17 is a potent proinflammatory molecule and may induce immune cell infiltration into affected tissues such as the skin and kidney [68]. IL-21 induced expansion and maintenance of Th17 cells may support IL-17 driven cellular inflammation and autoantibody responses in individuals with SLE.

Preclinical Evidence for a Role of IL-21 in the Pathogenesis of SLE

A potential role for the IL-21 pathway in the pathogenesis of lupus was first identified in BXSB-*Yaa* (Y chromosome-linked autoimmune acceleration) mice. These mice develop a chronic autoimmune disease that is characterized by lymphoid hyperplasia, monocytosis, hypergammaglobulinemia, and severe immune complex-mediated glomerulonephritis [73]. Disease pathology is due to a translocation of *Tlr7* from the X chromosome to the Y chromosome in these mice. Thus, chronic pathology is limited to male BXSB-*Yaa* mice [74,75]. IL-21 is elevated in the serum of BXSB-Yaa mice. Genetic deletion of IL-21R or neutralization of IL-21 with soluble IL-21R.Fc fusion protein in BXSB-*Yaa* mice resulted in increased survival, decreased serum Ig, and repressed expression of activation markers on B and T cells. Improved kidney function accompanied by tendency toward less severe MPGN and reduced number of kidney infiltrates was also observed, pointing towards a role for the IL-21 pathway in disease pathogenesis in BXSB-*Yaa* mice [76,77].

The role of IL-21 in the development of systemic autoimmunity has been studied most extensively in the MRL-Fas^{lpr} model. MRL-Fas^{lpr} mice fail to express Fas, a molecule required for the elimination of autoreactive T and B cells. As a result, MRL-Fas^{lpr} mice develop several hallmarks of SLE, including autoantibodies, hypergammaglobulinemia, lymphadenopathy, splenomegaly, dermatitis, arthritis and nephritis. Although IL-21 was not detected in the serum of MRL-Fas^{lpr} mice, CD4+ T cells isolated from these mice overexpress IL-21 when stimulated with anti-CD3 and anti-CD28 *in vitro* [78]. Neutralization of the IL-21 pathway reduced basal IgG and autoantibody titers, and reduced the severity and incidence of skin lesions, lymphadenopathy and splenomegaly in MRL-Fas^{lpr} mice. Blockade of the IL-21 pathway also prevented the development of nephritis in MRL-Fas^{lpr} mice as determined by reduced urine protein, and demonstrated reduced glomerular basement membrane thickening, glomerular Ig deposition, and immune cell infiltration upon histopathologic analysis [78,79].

It is not known how IL-21 blockade prevents disease in MRL-Fas^{lpr} mice, although there is evidence that IL-21 may support key pathogenic B and T cell responses in these mice [78]. Studies by Shlomchik et al. using MRL-Fas^{lpr} mice expressing IgH and IgL genes encoding an autoreactive B cell receptor have shown that autoantibody responses may primarily occur via an unconventional pathway outside of germinal centers at extrafollicular sites in the secondary lymphoid tissues of MRL-Fas^{lpr} mice [80,81]. Odegard et al have also identified a population of T cells at extrafollicular sites of B cell activation that produce IL-21 and support autoantibody production in MRL-Fas^{lpr} mice [22]. B cells isolated from MRL-Fas^{lpr} mice are hyperproliferative and overproduce IgG upon costimulation with IL-21 in combination with anti-IgM and anti-CD40 when compared to non-autoimmune strains [78]. IL-21 does not appear to be required for the activation or differentiation of B cells to isotype switched plasma cells at extrafollicular sites, but does enhance the magnitude and quality of these responses [82]. IL-21 also promotes the activation, differentiation, and expansion of T cells. CD4+ and CD8+ T cells both contribute to autoimmunity in this model, and neutralization of IL-21 reduced both CD4+ and CD8+ T cells in the spleens of MRL-Fas^{lpr} mice [78]. Th17 cells have also been recently shown to play a critical role in the development of multiple disease manifestations in MRL-Fas^{lpr} mice [69,70]. IL-21 may also be a key regulator of pathogenic Th17 responses in these mice although this has not yet been demonstrated.

In contrast to studies with BXSB-*Yaa* and MRL-Fas^{lpr} mice, studies with *sanroque* mice suggest that IL-21 is not necessary for the development of systemic autoimmunity. *Sanroque* mice contain a naturally occurring mutation in the roquin protein [83]. Roquin acts as a negative regulator of ICOS, a key regulator of TFH cell differentiation, function and IL-21 expression [84]. *Sanroque* mice spontaneously form a systemic lupus-like autoimmune disease characterized by the presence of isotype switched somatically mutated autoantibodies, accumulation of GCs and elevated serum IL-21 levels. Systemic autoimmunity in *sanroque* mice appears to be dependent on GCs, as deletion of Bcl-6, a transcription factor required for TFH and GC B cell differentiation, completely prevents development of disease in these mice [84,85]. IL-21 has been shown to be important for the induction of Bcl-6 in T and B cells, however, genetic deletion of IL-21R did not affect the formation of germinal centers or autoantibodies in *sanroque* mice, indicating that additional pathways control the development of systemic autoimmunity in these mice [86]. Collectively, these studies suggest that IL-21 can drive disease pathogenesis in lupus, but additional signaling pathways could also contribute to the disease.

Conclusion

Treatment of SLE has progressed very little over the past 50 years. One difficulty in the development of new therapeutics for SLE is the clinical heterogeneity of this disease. The modest improvements in the clinic for the treatment of signs and symptoms of lupus has demonstrated that B cells, and presumably autoantibodies, contribute to the pathogenesis of this disease [2]. However, it is likely that non-B cell mediated processes, such as those driven by T cells, also play a significant role in the pathogenesis of SLE. The contribution of the IL-21 pathway to the pathogenesis of SLE has yet to be demonstrated. The ability of this cytokine to regulate multiple aspects of both B and T cell responses, and drive systemic autoimmunity in animal models suggest that blockade of the IL-21 pathway may be a promising strategy for the treatment of SLE.

Acknowledgement

We thank Jacqueline Benson, M. Merle Elloso and Dave Shealy for reviewing this manuscript.

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This article was originally published in a special issue, **Cytokine Biology-Cytokines at the Interface of Health and Disease** handled by Editor(s). Dr. Joseph Larkin III, University of Florida, USA

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