Journal of Clinical & Experimental Pathology

Wang et al., J Clin Exp Pathol 2017, 7:5
DOI: 10.4172/2161-0681.1000323

Review Article Open Access

Biological Features of IL-12 and IFN- γ in the Pathogenesis of Systematic Lupus Erythematosus

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Received date: September 26, 2017; **Accepted date:** October 12, 2017; **Published date:** October 16, 2017

Abstract

Systemic lupus erythmatosus is a chronic autoimmune disease characterized by abnormal immune response with overproduction of auto-antibodies, self-destructive complexes and hyperactivity of both T and B lymphocytes. Although the exact pathogenesis of SLE remains unclear, it has been found that the imbalance of Th1/Th2, subsequent cytokines and anti- or pro-inflammatory mediators could reflect the stage and phenotype of SLE. Among diverse cytokines involved in the disease progression, IL-12 and IFN-γ gain much attention for their biological functions in SLE. There existed many divergences on the expression level of IL-12 while few conflicts were demonstrated on elevated level of IFN-γ in SLE patients. By analysis of gene polymorphisms, it was suggested that positive correlations were observed between IL-12B rs3212227, IL-12B rs17860508 and susceptibility to and severity of SLE in Polish patients. In addition, the combination of the IL-12B rs17860508 GC allele and/or IL-12B rs3212227 C allele could increase the risk of SLE progression and/or severity of SLE parameters in Polish population. Furthermore, it was also found that the incorporation of IFN-γ R_1 Met 14/Val 14 and IFN-γ R_2 Gln 64/Gln 64 genotypes was a potential risk factor for SLE. Based on the previous researches, IL-12 and IFN-γ targeted gene therapy was developed and found to be effective in murine lupus. Intramuscular injection of IFN-γR/IgG1Fc fusion protein encoded cDNA and suppressive ODN was found to decrease the severity of disease and promote survival of lupus mice. On the other hand, intramuscular injection of IL-12 and IL-18 encoded plasmids alone or together was also observed to have therapeutic effects on murine lupus. All in all, this review mainly introduces the biological features and the potential therapeutic effects of IL-12 and IFN-γ in the pathogenesis of SLE.

Keywords: Systemic lupus erythmatosus; Interleukin-12; Interferon-gamma; Pathogenesis

Introduction

Systemic lupus erythmatosus (SLE) is a representative multisystem autoimmune disease, characterized by abnormal immune response including overproduction of auto-antibodies, deposition of immune complexes and hyperactivity of both T and B lymphocytes, exerting severe damage to multiple organs and connective tissues in large population throughout the world [1]. Owing to genetic predisposition and environmental factors, SLE mainly occurs in child-bearing period female with gender distribution of 9:1 to male [2]. SLE is a heterogeneous autoimmune disorder with diverse clinical manifestations ranging from subtle skin lesion to severe multisystem dysfunctions including pericarditis, respiratory distress, osteoporosis and renal failure [3]. With its unpredictable manifestations and extensive organ injuries, investigators tried to figure out the paradigm of bio-markers fluctuation in SLE to evaluate susceptibility and progression of the disease, which could be used to make treatment decisions at the early stage of disease and decrease the damage to SLE patients [4].

Several decades of research into SLE blood markers has generated few widely accepted biomarkers including double-stranded DNA (ds-DNA), complement and auto-antibodies for prediction, diagnosis and treatment. Benefit from these traditional biomarkers, standards including SLE activity index (SLEDAI), systemic lupus activity measure (SLAM) and British Isles Lupus Assessment Group (BILAG) were developed to evaluate SLE while its extensive organ coverage brought inconvenience to routine clinical practice [5]. With the advance of cell signaling profile in SLE, a series of non-traditional and emerging biomarkers including cytokines, growth factors, chemokines and acute phase reactants were found to have potential clinical effects in SLE. Diverse characteristics and introduction of traditional and non-traditional biomarkers for SLE were described elsewhere [6]. Cross communications among various cells, especially immune cells, play vital roles in the pathogenesis of SLE and cytokines gain much attention for their abilities to mediate adjacent and long-distance communications among immune cells. A great number of studies have addressed the expression profile of Th1 or Th2-related cytokines in SLE and tested the biological effects in animal lupus models following the knockdown or overexpression of these cytokines [7].

According to previous reports, interferon-α (IFN-α), soluble interleukin-2 receptor(sIL-2R) and soluble tumor necrosis factor receptor (sTNFR) were thought to be potential biomarkers of SLE; IL-1Ra, IL-6, IL-10, IL-12p40, IL-13, IL-16, IL-18 and TNF were found out to have possible effects while IFN-γ, IL-12 and IL-15 were not promising to be biomarkers of SLE [8]. Though IL-12 and IFN-γ may not be proper biomarkers for clinical diagnosis, the results of researches on them triggered switching of Th1/Th2 mediated immune trend and their targeted therapies were proved to be effective in

murine lupus [7,9]. Besides, abnormal expressive forms of IL-12 and IFN-γ were universally reported and contradictory data were collected among different ethnicities and regions. No consensus has been reached yet partly due to insufficient researches and there were few papers that systematically demonstrated the observation of IL-12 and IFN-γ though the two cytokines were closely related to each other in expression profile. Type I IFN-targeted therapy including monoclonal antibody of IFN-α and its receptor have completed phase II and III clinical trials while other IFNs, such as IFN-γ, and recently discovered type III IFNs were still tested in animal models [10]. Therefore, this review was conducted to demonstrate the present findings and divergences of IL-12 and IFN-γ in SLE and summarize novel targeted therapies of the two cytokines, which can be a rough knowledge basis for further researches on cytokines in SLE.

IFN-γ and its regulatory roles in SLE

Interferon-gamma (IFN-γ), as one kind of water-soluble dimer cytokine is the only member of type II interferon, initially called macrophage activation factor. The biologically active IFN-γ is formed by two anti-parallel interlocking monomers, which is composed of six alpha helices consisting of one core and a fragment sequence extending at the C-terminal region. IFN-γ is a typical kind of cytokine secreted by Th1 cell and its expression profile is regulated by a series of IFN-inducing factors including IL-12, IL-15 and IL-18. It was reported that serum levels of IFN-γ in lupus patients were higher than in controls [11-14]. Min et al. investigated the associations between IFN-γ and lupus nephritis, and defective IFN-γ production was observed in 17 patients with lupus nephritis compared with 23 patients with un-nephritic lupus. A subtle correlation was found between SLEDAI scores and serum IL-4/IFN-γ ratios [15]. No distinctions in mitogen-stimulated and phytohemagglutinin-induced IFN-γ levels were observed between patients and healthy controls in some literatures. However, evident correlation of IFN-γ with SLAM scores was reported in other studies [16,17]. Apart from directly evaluating the IFN-γ levels in patients and controls, researchers also detected some downstream products of IFN-γ. With the stimulation of IFN-γ, enzyme indoleamine dioxygenase (IDO), which can transform tryptophan into kynurenine, is further converted to final substances like nicotinamides and quinolinic acid. Widner et al. detected the levels of serum tryptophan, kynurenine and the kynurenine/tryptophan quotient (K/T) in 55 SLE patients in order to know the enzyme activity of IDO. Compared with healthy donors, there were lower tryptophan levels and higher kynurenine levels and K/T quotients in SLE patients. Besides, a slight correlation between K/T quotients and SLEDAI scores was established [18]. Polymorphisms of IFN-γR1 and R2 have been found in some lupus patients, and incorporation of IFN-γR1 Met14/Val14 and IFN-γR2 Gln64/Gln64 genotypes has been demonstrated to be a potential risk factor for SLE [19]. Nonetheless, with the mitogenic stimulation, higher expression levels of IFN-γ were detected from mononuclear cells in peripheral blood of lupus patients than controls [20]. It is very interesting to find that some patients would suffer from severe lupus-like disease, if they were treated with IFN-γ for unrelated autoimmune diseases [21,22].

In recent years, a variety of techniques have been applied to measure the expression levels of cytokines in lymphoid organ and tissue in mouse models of SLE [23]. Elevated IFN-γ levels were detected in the MRL-Fas^{lpr} lupus mice especially at the late stage of disease [24-29]. Transgenic mice with over-expressed IFN-γ would develop T-cell dependent lupus-like syndrome and deposits of antinuclear auto-antibodies in kidney [6,30]. Jacob et al. firstly came up with the idea that IFN-γ played an important role in the pathogenesis of lupus [31]. In this study, they found that conditions were aggravated in (New Zealand Black (NZB) × New Zealand White (NZW)) F1 (B × W) lupus mice that were treated with IFN-γ or its inducers, while the onset of SLE was delayed in those receiving anti-IFN-γ antibody at an early stage. Following these findings, Ozmen et al. treated lupus mice with soluble IFN-γ or recombinant IFN-γ R, or with anti-IFN-γ antibody. They found longer overall survival and decreased histologic and serologic parameters of lupus in B × W mice receiving sIFN-γ R or anti-IFN-γ. By contrast, those with the treatment of IFN-γ died earlier than controls. Moreover, only if all the mice were treated with anti-IFN-γ antibody or sIFN-γ R at the early stage of lupus disease were the treatments effective. The reason might be that the very high levels of the ligand formed late in the disease process could not be completely neutralized [32]. However, other studies indicated that application of monoclonal IFN-γ antibody exerted no influence on disease severity and mortality of MRL-Fas^{lpr} mice [33]. Transgenic mice that IFN-γ and IFN-γR genes were deleted were used to research the role of IFN-γ in lupus. In the study, it was found that survival and disease parameters significantly decreased. Besides, hypergammaglobulinemia with transition from IgG2a to IgG1 predominance was detected in IFN-γ-deleted transgenic lupus mice while the subclass of IgG1 anti-dsDNA auto-antibodies did not increase with the decreased levels of IgG2a anti-dsDNA auto-antibodies. Moreover, it was found that the progression of glomerulonephritis and rate of early death were suppressed even in heterozygous IFN-γ deleted lupus mice which were reduced by 50% in IFN-γ expression but not in auto-antibody and immune complexes in kidney [34,35]. In summary, all these findings suggest that IFN-γ may promote lupus progression in both humor-mediated and cell-mediated manners (Figure 1).

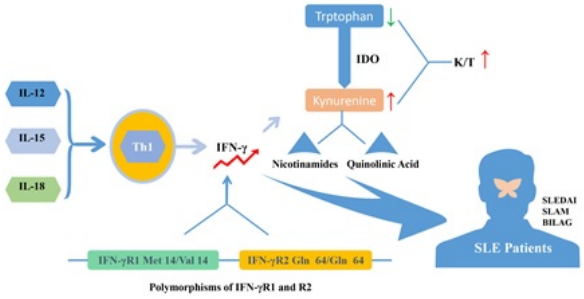

Figure 1: IFN-γ and its regulatory roles in SLE.

IL-12 and its regulatory roles in SLE

IL-12, a 70-kDa heterodimer secreted by activated dendritic cells and macrophages, stimulates early helper T cells to differentiate into Th1 cells and promotes the development and proliferation of Th1 cells *via* signal transducer and activator of transcription 4 (STAT4). IL-12 can induce IFN-γ production in T helper type 1 (Th1) cells *via* IL-1 receptor-related kinase pathway together with IL-18, resulting in nuclear translocation of the NF-κB complex [36]. Therefore, IL-12 promoted synthesis of IFN-γ and generation of Th1 cells while it suppressed progression of Th2 cells [37,38]. Past investigations have well documented the regulation of IL-12 *in vitro*, which positively correlated with elevated levels of IFN-γ and could be inhibited by IL-10 and IL-4 [39,40]. Serum IL-10 positively correlated with anti-ds DNA antibody, an significant marker presenting in 70% of SLE

patients, while IL-12 was reported to negatively correlate with anti-ds DNA antibody [41]. It was suggested that the serum levels of IL-12 in active SLE patients were higher than in the controls in some studies while other investigators found defective IL-12 production in lupus patients [36,42]. IL-12 is composed of p35 (IL-12A) and p40 (IL-12B) and the two subunits are homologous to EBs and P28, two components of IL-27, which have both pro-inflammatory and anti-inflammatory effects on the pathology of autoimmune disease and play diverse roles in Th cell responses [43,44]. Since gene polymorphisms could modify the expression profile of cytokines, investigators began to study the association between polymorphisms of IL-12 and IL-27 and progression of SLE. In these studies, they found that there existed positive correlations between IL-12B rs17860508 and susceptibility to and severity of SLE, and IL-12B rs3212227 positively correlated with severity of SLE in Polish patients. Besides, the combination of the IL-12B rs17860508 GC allele and/or IL-12B rs3212227 C allele increased the risk of SLE and/or the severity of SLE parameters in Polish population [45]. Other studies have showed that C allele in IL-12B 3′ UTR connected with higher production of IL-12p70 while GC allele in IL-12B promoter binding with Sp1 increased gene transcription and cytokine activity [46-52]. All these alleles might increase the levels of IL-12 and affect the immune response *via* regulation of T cell activity, resulting in abnormalities in SLE. However, Sanchez, et al. investigated the IL-12B polymorphisms mentioned above in SLE patients and did not find the relationships between these SNPs and the predisposition to SLE or the progression of lupus nephritis in the Spanish population [53]. Hirankarn et al. demonstrated that the A allele and A/A genotype of IL-12 at 3′ untranslated region in SLE patients had few associations with proteinuria in Thais population [54]. Discrepancies among reports of IL-12 gene polymorphisms might be explained by the heterogeneity of different diseases, distinct ethnicities, limited sample size and diverse genotyping methods. Some reports revealed that serum levels of IL-12 were uncorrelated with disease activity while its p40 subunit was correlated with SLEDAI scores and immunosuppressive therapy could downregulate the levels of this subunit of IL-12 [55-57]. Min et al. investigated the associations between IL-12 and lupus nephritis, and they observed defective IL-12 production in 17 patients with lupus nephritis compared with 23 patients with un-nephritic lupus [15]. Except for defective IL-12 production, hyperproduction of IL-6 and IL-10 was detected *via* a series of studies on SLE [58,59]. On the other hand, as for these SLE patients with increased IL-12 and IFN-γ, they were also found to have higher Th1/Th2 ratios in the peripheral blood mononuclear cells. Predominance of Th1 cells in the blood and kidneys was particularly potent in patients with diffuse proliferative nephritis [60]. Apart from IFN-γ, elevated levels of IL-12 were also detected in the kidney-infiltrating mononuclear cells and tubular epithelial cells of MRL-Fas^{lpr} mice, a model of murine lupus (Figure 2) [61-63].

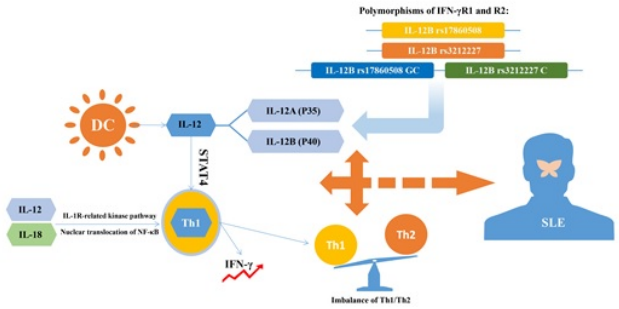

Figure 2: IL-12 and its regulatory roles in SLE.

IL-12 and IFN-γ targeted therapy for SLE

Systemic lupus erythmatosus is an auto-immune disease with a malfunction of self-tolerance that causes a variety of severe system disorders. Past investigations have clearly addressed the complexity of cellular and humoral abnormalities under the influence of environment, predisposing gene and sex hormone in both animal models and patients. In clinical practice, immunosuppressant (e.g., cyclophosphamide, tacrolimus and prednisolone) and NSAIDs (nonsteroidal anti-inflammatory drugs) were widely used and proved to be effective in both treatment and prevention. However, severe adverse effects including infertility, infection and amenorrhea frequently occurred and exerted immense sufferings on SLE patients. Therefore, based on the profile of cytokine imbalance, a series of novel therapies including B lymphocyte inhibition, costimulation supression and cytokine antagonists were developed [64,65]. The damages of diverse organ and tissue are caused by different immune responses in SLE. The hormonal factors closely related to capillary damage in glomeruli, lungs, dermal tissues while damage for interstitium of kidneys, lacrimal, and salivary glands were caused by cell-mediated immunity [66,67]. Therefore, investigators thought single cytokine-targeted therapy might not be adequate because of complex cytokine network but a certain cytokine targeted therapy had potent effects with cascade reaction of immune response. Here we mainly introduce IL-12 and IFN-γ targeted therapy for SLE may simplify the treatment. Although the results of IL-12 and IFN-γ targeted therapy are proved to be effective in animal models, whether its therapeutic effects remain the same in patients still needs further clinical studies to certify.

IFN-γ targeted therapy: Since studies of diverse levels showed the therapeutic effects of IFN-γ suppressing methods in murine lupus, intramuscular injection of a non-viral vector with IFN-γR/IgG1Fc fusion protein encoded cDNA has been regarded by investigators as a novel method to interfere IFN-γ expression [68]. Different from truncated IFN-γ receptor, fusion compound was a kind of disulfide-linked homodimer possessing longer T1/2 and higher avidity [69]. By treatment with IFN-gR/Fc vector before symptoms appeared, serum levels of IFN-γ and parameters in lupus would effectively decrease in MRL-Fas^{lpr} mice. Moreover, even at the early stage of disease, this kind of treatment could still make a difference. It was infrequent to find that suppression of single target had significant effects on this chronic immune disease with various pathogenic factors [46,70]. Until now, the mechanism how the blockade of IFN-γ reduces the deterioration of murine lupus has not been fully understood. One possible explanation was that suppression of IFN-γ lead to reduction of MHC class I and II

molecules in renal tubular epithelial and mononuclear cells, destroying self-peptide presentations and responses [47]. Besides, a series of pro-inflammatory factors like monocyte chemattractant protein-1 and intercellular adhesion molecule 1 have also been detected to be suppressed following the down regulation of IFN-γ [48]. Compared with viral vectors, it was simple to finish intramuscular injection of plasmid vector of IFN-γR/IgG1Fc with higher safety and lower toxicity [49]. Moreover, this gene targeted therapy permits long-term production of fusion protein and migration of injected DNA to other organs, which have advantages over the usage of sIFN-gR.

Past studies have revealed that synthetic oligodeoxynucletides (ODN) with TTAGGG motif, which highly accumulated in telemeric region of mammalian chromosomes, could be suppressed to treat autoimmune disease [50-52]. Sano et al. reported that ODN without CpG motifs functioned as an adjuvant to induce Th2 differentiation and Dong et al. reported that glomerulonephritis and survival of lupus mice model were improved by synthetic ODN with significant reduction of anti-ds DNA auto-antibody, IL-12, IFN-γ and IL-6. Besides, they also tested whether ODN had negative effects on animal well-being, which was measured by body weight and general activity, and made a conclusion that no obvious impairments were observed. Therefore, suppressive ODN may be an ideal method to treat autoimmune disease like SLE. However, the mechanism how ODN suppression influences inflammatory immune responses still needs further investigation. It was reported that ODN suppression blocked the signal pathway which could regulate the production of IL-12 and IFN-γ, causing the balance of Th1/Th2 changed [71-73].

IL-12 targeted therapy: Hagiwara et al. explored the therapeutic effects of IL-12-encoding plasmid on lupus according to the former concept that lupus was a Th2 related disease for shifting polarized immune response from Th2 to Th1. Murine lupus model was established and all mice were treated with IL-12-encoding plasmid DNA *via* intramuscular injection every 4 weeks at age of 4 weeks. Results demonstrated that accumulation of CD4 (−) CD8 (−) T cells was greatly inhibited accompanying with reduced splenomegaly and lymphadenopathy. Besides, it was also found that severity of glomerulonephritis and proteinuria weakened and serum IgG anti-DNA auto-antibody titers reduced while serum levels of IFN-γ increased. Therefore, the balance of cytokines tended to Th1 but the mechanism of this intervention was not totally depended on an IFN-γ-mediated pathway [74,75].

It has been reported that injection of recombinant IL-12 or IL-18 proteins might aggravate the lupus-like symptoms in lupus mice, and elevated serum levels of IL-12 and IL-18 were observed in SLE patients [14,76-79]. Neumann et al. conducted intramuscular injection of IL-12 and IL-18 encoded plasmids alone or together on specific mouse models of SLE over expressing both TNF-γ and IFN-γ. Through the study, they observed decreased serum levels of TNF-γ and weakened productive ability of lymphocytes to produce IFN-γ *in vitro*. Synergistical injection of two plasmids not only attenuated the severity of lupus syndromes, lymphoproliferation in secondary lymphoid organs but also relieved proteinuria, kidney damage, and pneumonitis with decreased serum TNF-α concentration. Cells from lymph node secreted fewer levels of IFN-γ in IL-12/IL-18-treated mice while anti-dsDNA IgG levels were not affected (Figure 3) [80].

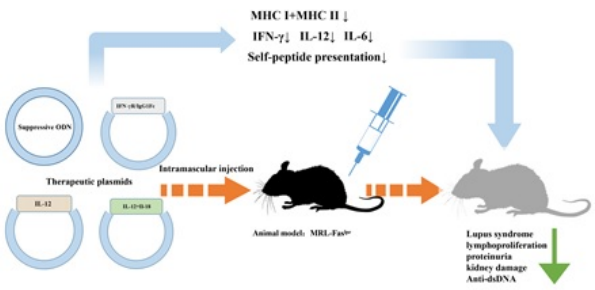

Figure 3: IL-12 and IFN- γ targeted therapy for SLE.

Summary

The imbalance of cytokines plays an important role in the pathogenesis of systemic lupus erythematosus with elevated levels of auto-antibody, deposits of complement and activation of immune responses [81,82]. Among various cytokines overexpressed or suppressed in SLE, abnormal production of IL-12 and IFN-γ gained much attention in old researches. Nevertheless, conflicts on IL-12 expression profile in SLE patients have been arising. Some studies demonstrated that IL-12 was upregulated in serum of patients at the active stage of SLE, while others reported defective IL-12 production in lupus patients [36,42]. As for IFN-γ, divergences were not so obvious and past literatures tend to suggest that serum levels of IFN-γ were higher in lupus patients than in controls [10-15]. In addition, IFN-γ was also associated with symptomatology of SLE, in which a subtle correlation was found between SLEDAI scores and serum IL-4/IFN-γ ratios and evident correlation of IFN-γ with SLAM scores was also documented [16,17]. Based on clinical discoveries, murine lupus model was applied to explore the internal mechanism and potential therapeutic effects. Treatment of IFN-γ or its inducers accelerated the lupus progression while IFN-γ antibody, recombinant IFN-γR presented longer overall survival and decreased histologic serologic parameters of lupus and significantly delayed lupus onset in B × W lupus mice [10].

Apart from clinical and animal studies, researches of gene polymorphisms were also performed and positive relationships between IL-12B rs3212227, IL-12B rs17860508 and susceptibility to and severity of SLE in Polish patients were observed. In addition, the combination of the IL-12B rs17860508 GC allele and/or IL-12B rs3212227 C allele increased the risk of SLE progression and/or severity of SLE parameters in Polish population [45]. Moreover, incorporation of IFN-γR_1 Met14/Val14 and IFN-γR_2 Gln64/Gln64 genotypes has been explored to be a potential risk factor for SLE. Based on the biological features of IL-12 and IFN-γ, scientists have developed the gene therapies aiming to correct IFN-γ and IL-12 expressive profile and have found their effects were promising in murine lupus. Intramuscular injection of IFN-γR/IgG1Fc fusion protein encoded cDNA and suppressive ODN were found to attenuate the severity of disease and promote survival of lupus mice. On the other hand, it was also found that intramuscular injection of IL-12 and IL-18 encoded plasmids alone or together had therapeutic effects on murine lupus. In general, abnormal expression of IL-12 activate Th1 cells and trigger upregulation of IFN-γ from Th1 cells towards Th1-predonminant immunity, causing subsequent production of autoantibodies and

complements in SLE. On the other hand, gene polymorphisms of IL-12 and IFN-γ may partly describe the abnormal production of IL-12 and IFN-γ. Considering the severe adverse effects of classic immunosuppressant, IL-12 and IFN-γ targeted gene therapies were established and proved to be effective in murine lupus while multi-center clinical trials still need further progression.

Acknowledgements

This study was supported by Grants National Natural Science Foundation of China (No.81573217, 81172764), and Scientific Research of BSKY from Anhui Medical University (No. XJ201301).

Conflict of Interest

The authors declare no conflict of interest.

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