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Rationale for interleukin-6 blockade in systemic lupus erythematosus

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Abstract

Interleukin-6 (IL-6) is a pleiotropic cytokine with a wide range of biological activities that plays an important role in immune regulation and inflammation. Among other actions, it induces terminal differentiation of B lymphocytes into antibody-forming cells and the differentiation of T cells into effector cells. IL-6 also has multiple potent proinflammatory effects. An association between IL-6 and lupus was demonstrated in murine models of SLE and blocking IL-6 improved lupus in all models tested. Data from several studies suggest that IL-6 plays a critical role in the B cell hyperactivity and immunopathology of human SLE, and may have a direct role in mediating tissue damage. Based on these data, we propose that blocking the effect of IL-6 in humans may improve lupus by interacting with the auto inflammatory process both systemically and locally.

Keywords

autoimmunity; biologic therapy; cytokines; experimental treatment

Introduction

In systemic lupus erythematosus (SLE), an initial breakdown in tolerance creates primary autoreactive effectors which then propagate the autoimmune response by a variety of mechanisms that probably include positive feedback amplification loops. Auto-antibody production, complement activation, immune complex deposition, and leukocyte infiltration of target organs are key immunopathogenic events. Cytokine production in SLE differs from that in both healthy individuals and patients with other rheumatic diseases, such as rheumatoid arthritis. Cytokines have been implicated in regulating disease activity and in the involvement of different organs in patients with SLE.

Interleukin-6 (IL-6) and its receptor (IL-6R)

IL-6

IL-6 is a pleiotropic cytokine with a wide range of biological activities.¹ It acts in an endocrine, autocrine and paracrine fashion on a diverse number of target cells. The major sources of IL-6 are monocytes; fibroblasts and endothelial cells, but T cells, B cells, keratinocytes, mesangial cells, and several tumor cells also produce IL-6. Its synthesis is induced by IL-1, IL-2, tumor necrosis factor (TNF- α), and interferons (IFN)- and is inhibited by IL-4, IL-10 and IL-13. IL-6 plays an important role in immune regulation and inflammation as well as autoimmune diseases. One of the most important biologic actions of IL-6 is its ability to stimulate the final stages of B lymphocyte maturation. Under the influence of IL-6, B lymphocytes differentiate into mature plasma cells and secrete immunoglobulins (Ig). In addition, IL-6 induces T cell

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growth and cytotoxic T cell differentiation through augmentation of IL-2 receptor expression and IL-2 production. IL-6 synergizes with other cytokines to support bone marrow stem cell maturation, is a neutrophil activator and stimulates the production of platelets from megakaryocytes. It is also a potent inducer of terminal macrophage and osteoclast differentiation. IL-6 also shares several activities with IL-1 and TNF, including the induction of pyrexia and the production of acute phase proteins such as serum amyloid A, CRP, alpha 1 antitrypsin, fibrinogen, and haptoglobin. In contrast to these proinflammatory effects, IL-6 mediates several unique anti-inflammatory effects. Whereas both IL-1 and TNF- α induce synthesis of each other, as well as IL-6, IL-6 terminates this upregulatory inflammatory cascade and inhibits IL-1 and TNF- α synthesis. It is also important that, as a cell growth factor, IL-6 can induce the proliferation of epidermal keratinocytes and mesangial cells and has an active role in mesangial proliferative glomerulonephritis.

The receptor for IL-6 (IL-6R) belongs to the type I cytokine receptor superfamily and consists of two chains, namely IL-6R, an 80 kDa glycoprotein and gp130. IL-6R is the ligand specific binding component while gp130 is a shared receptor component responsible for transmitting intracellular signals of IL-6 related cytokines such as leukemia inhibitory factor (LIF), ciliary neurotropic factor, oncostatin M and IL-11. IL-6 binding to the receptor leads to dimerization of gp130, resulting in the activation of gp130 associated kinase JAK1 and subsequently tyrosine phosphorylation of gp130. Whereas gp130 is ubiquitously expressed, IL-6R is more restricted. Both IL-6R and gp130 have soluble forms. The complex of IL-6 and soluble IL-6R can act on cells expressing only gp130; this is potentially an important proinflammatory mechanism for soluble receptors. However, it is not yet clear whether soluble IL-6R acts positively on gp130 signaling under physiological conditions.¹

Interleukin-6 in systemic lupus erythematosus

Interleukin-6 and IL-6 blockade in murine models

An association between IL-6 and progression of lupus has been published for several murine models of SLE (Table 1). Age associated increase of serum IL-6, soluble IL-6R and abnormal expression of the IL-6R have been described in MRL/lpr mice.²⁻⁴ These findings may contribute to development of B cell hyper-reactivity and T cell abnormality in this model. In NZB/W mice anti-IL-6 antibodies reduced, and exogenous IL-6 increased *ex vivo* production of IgG ds-DNA antibodies by B cells from old but not young B/W mice.⁵⁻⁸ Apart from IL-6, no other lymphokine tested was shown to be capable of directly inducing the production of IgG anti-DNA antibodies. The direct role of IL-6 in controlling autoantibody production was demonstrated in the pristane induced model of lupus. The pristane induced IgG autoantibody production against chromatin, single-stranded DNA and double stranded DNA observed in wild type mice was blocked in IL-6 deficient mice. In contrast, the frequency of anti-RNP/Sm and anti-Su antibodies was similar in IL-6-deficient and intact animals, suggesting a different cytokine requirement of different subsets of lupus associated autoantibodies and a direct role of IL-6 in the generation of anti-DNA antibodies.⁹

In another study, exogenous administration of recombinant human IL-6 (rhIL-6) to female NZB/W mice accelerated the progression of glomerulonephritis.¹⁰ Although there was no difference in the levels of anti-dsDNA antibody levels, IL-6 treated animals had accelerated proteinuria, developed a more severe form of glomerulonephritis and had dose dependent increases in mortality. Cyclosporine A blocked the effect of exogenous IL-6, suggesting that the effect of IL-6 is through its immunomodulatory effects and is not a direct effect on mesangial cells.¹⁰ Similarly, in BXSB mice, intramuscular injection of an IL-6 expressing vector led to increased expression of IL-6 in the kidney, accelerated production of autoantibodies and worse proteinuria.¹¹

The most compelling evidence supporting the direct involvement of IL-6 in the pathogenesis of lupus nephritis was demonstrated by the beneficial effect of IL-6 blockade in NZB/W mice. Chronic administration of a rat anti-IL-6 monoclonal antibody¹² or rat anti-IL-6 receptor antibody¹³ starting at three months of age prevented age related increases in anti-dsDNA antibody levels, progression of proteinuria and significantly improved mortality.

IL-6 in human SLE

Data from several studies suggest that IL-6 plays a critical role in the B cell hyperactivity and immunopathology of human SLE, and may have a direct role in mediating tissue damage (Table 1). Lupus patients have elevated levels of serum IL-6^{14–16} that correlated with disease activity¹⁵ or anti-DNA levels¹⁴ in some, but not all studies.¹⁶ Compared to healthy controls SLE patients had significantly higher frequency of IL-6 secreting PBMCs,¹⁷ lymphoblastoid cells isolated from lupus patients produced higher levels of IL-6 and blocking IL-6 inhibited anti-dsDNA production *in vitro*.¹⁸ However, IL-6 production in LPS stimulated whole blood culture was lower in SLE patients compared to normals in another study.¹⁹

Unlike in normals, B cells from lupus patients spontaneously produce large amounts of immunoglobulins; neutralization of IL-6 led to a significant decrease in this spontaneous Ig production which was restored with exogenous IL-6.¹⁵ Lupus B cells also produce anti-DNA antibodies spontaneously; however, different B cell populations contribute to this in different ways. The majority of antibodies are produced by low density B cells while high density B cells have little effect on autoantibody production *ex vivo*.²⁰ IL-6 effectively differentiates preactivated, low density B cells into Ig secreting cells, but only low density B cells from patients with active lupus are capable of directly differentiating into Ig secreting cells in response to IL-6.²¹ B cells from lupus patients produce large amounts of IL-6 and express IL-6R spontaneously.^{21,22} In fact, the expression of IL-6R was shown to be present only on low density B cells from patients with active but not inactive lupus or healthy controls. These results suggest that, in SLE, B cells express higher levels of IL-6 that can bind to the IL-6R expressed on low density B cells from active lupus patients and induce terminal differentiation and increased autoantibody production in these *in vivo* preactivated B cells.²⁰ These results also suggest that deregulation of B cell activity in SLE could, at least in part, be T cell independent.²² On the other hand, autoreactive T cell clones from lupus patients activated by anti-CD3 and PMA secrete multiple Th1 and Th2 cytokines, of which only IL-6 was consistently produced by all the T-cell clones.²³

Adding an anti-IL-6R monoclonal antibody to cultures of autoreactive T cells and autologous B cells led to a profound reduction in IgG anti-DNA antibody secretion. These results suggest that autoreactive T cells in lupus produce higher levels of IL-6 and facilitate the production of autoantibodies.²³ Alternatively, IL-6 may have an effect on the activity of suppressor T cells as suggested by two recent papers. Decreased activity of CD8⁺ suppressor T cells was demonstrated in active lupus patients when compared to healthy controls and patients with inactive disease.²⁴ Lupus patients secreted lower amounts of IL-6 and blocking IL-6 secretion with an anti-sense oligonucleotide decreased the *in vitro* suppressor activity of CD8⁺ T cells.²⁴ In mice, however, IL-6 rendered pathogen specific T cells refractory to the suppressive activity of CD4⁺ 25⁺ regulatory T cells.²⁵ This observation may, at least in part, explain that IL-6 deficient mice are resistant to autoimmune diseases, such as experimental autoimmune encephalitis, rheumatoid arthritis and colitis.^{26–29}

Since a number of cytokines with often opposing primary effects are elevated in lupus patients it is important to determine if the elevated IL-6 level observed in these patients is due to an intrinsic defect or if it is an acquired phenotype. Exogenous IL-10 and IL-4 mediated reduction of IL-6 in monocytes of SLE patients as effectively as that of controls. However, IL-10 affected IL-6 only when given close to activation, and because of its differential time kinetics and

availability it may be less effective *in vivo* in reducing IL-6 production. IL-10 also down-regulated monocyte derived cytokines that upregulate IL-6, such as TNF- α ; therefore, IL-10 affects IL-6 production directly as well as indirectly. PBMCs from active lupus patients had higher levels of IL-6 mRNA than inactive SLE patients and healthy controls and decay of IL-6 mRNA was significantly delayed in active patients. IL-6 mRNA degradation was accelerated in the presence of anti-TNF- α or IL-1 β antibodies or by rIL-10, but not by IL-4 or TGF- β . These results suggest that IL-6 mRNA levels are higher in PBMCs of patients with active lupus due, at least in part, to delayed decay of IL-6 mRNA. Some cytokines, such as IL-4, have an effect on IL-6 production at the transcriptional level while others such as IL-10 act posttranscriptionally. Since SLE PBMCs respond normally to regulatory signals *in vitro*, the overexpression of IL-6 in lupus reflects, at least in part, the kinetics and availability of regulatory cytokines.³⁰

It cannot completely be ruled out, however, that the IL-6 abnormalities observed in SLE may be due, at least in part, to genetic differences. An adenosine/tyrosine rich minisatellite located in the 3' flanking region of the IL-6 gene was found to have significant different allele frequencies between SLE patients and controls, both in Caucasian and African-American populations.³¹ A short allele was only present among patients, whereas a longer allele was overrepresented in the controls, showing a strong association of the shorter allele with SLE in both ethnic groups. Furthermore, in lupus patients having SLE associated minisatellite alleles, B lymphoblastoid cells secreted IL-6 in three- to four-fold higher levels, higher percentages (approximately four-fold) of IL-6 positive monocytes were observed and IL-6 mRNA stability was significantly enhanced suggesting that the 3' minisatellite alleles have biological significance.³¹

Anti-double stranded DNA antibodies are the marker autoantibodies in systemic lupus erythematosus. Although the titer of anti-dsDNA antibodies in the serum can reflect disease activity in lupus nephritis, the exact role of these autoantibodies remains unclear. They can bind with DNA or DNA-histone conjugates to form circulating immune complexes and deposit in the tissues to elicit inflammation. In addition, anti-dsDNA autoantibodies can have a direct effect on cytokine expression in various cells. Anti-dsDNA autoantibodies upregulate the expression of the proinflammatory cytokines IL-1 and IL-6 in endothelial cells,³²⁻³⁴ and stimulate the expression and release of IL-1, IL-6, IL-8, IL-10 and TNF from normal human resting mononuclear cells.³⁵ Since IL-6 increases the secretion of anti-dsDNA autoantibodies this may lead to a paracrine upregulation of both IL-6 and anti-dsDNA.

IL-6 and lupus nephritis

Mesangial cell proliferation is one of the hallmarks of proliferative lupus nephritis. Several studies suggested that IL-6 has proliferative effects on mesangial cells and thus might be capable of modulating injury in immunologically mediated nephritis. IL-6 plays a role in the pathogenesis of mesangial proliferative glomerulonephritis (mesPGN) and IgA nephropathy. Urinary IL-6 levels correlate well with mesangial proliferation in mesangial proliferative glomerulonephritis^{36,37} and progression of IgA nephropathy³⁸ (Table 1).

Several studies have demonstrated increased urinary excretion of IL-6 in patients with active lupus nephritis. Urinary IL-6 levels were higher in patients with proliferative lupus nephritis (World Health Organisation Class III and IV) who had high titers of anti-dsDNA antibodies^{39,40} and in patients with active nephritis compared to inactive nephritis patients.^{16,40} IL-6 excretion decreased following treatment with cyclophosphamide. Increased *in situ* expression of IL-6 was demonstrated in lupus nephritis along the glomeruli and the tubules.⁴¹⁻⁴³ Infiltrating inflammatory cells, mainly monocytes/macrophages, are the major source of IL-6 in the kidney in lupus nephritis;⁴³ however, mesangial cells also produce IL-6 in lupus nephritis but not in noninflammatory kidney diseases or in normal kidneys.⁴⁴ We have shown

that CD40 ligand activated human monocytes induce synthesis of high levels of IL-6 in mesangial cells through both soluble factors and cell to cell contact⁴⁵ while others have shown that anti-dsDNA antibodies upregulate IL-6 expression in mesangial cells.⁴⁶ These data suggest that IL-6 may have an important role locally in lupus nephritis. Both activated inflammatory cells and resident renal cells are capable of producing and responding to IL-6. In addition, anti-dsDNA antibodies can further enhance IL-6 production locally. The decrease in the abnormally increased local IL-6 expression in the kidney following effective treatment suggests that blocking IL-6 may be beneficial.

In summary, IL-6 has an important role in maintaining the autoinflammatory loop in systemic lupus erythematosus. IL-6 levels are elevated in both human and murine lupus and blocking IL-6 or its receptor had beneficial effect in all models of lupus tested to date. Based on these data, we propose that blocking the effect of IL-6 in humans will lead to a decrease in anti-dsDNA antibodies through the blockade of terminal differentiation and improvement in the clinical symptoms of lupus by interacting with the autoinflammatory process both systemically and locally. A phase I clinical study using an anti-IL6R monoclonal antibody is under way to address some of these questions.

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Table 1

Rationale for IL-6 blockade in SLE

Murine models of SLE	<p>Age related increase in serum IL-6 and soluble IL-6R levels Abnormal expression of IL-6R IL-6 increases autoantibody production Blocking IL-6 decreases autoantibody production Anti-dsDNA antibody production was blocked in IL6 -/- mice Exogenous IL-6 accelerated the progression of glomerulonephritis Blocking IL6 prevented age related increases in anti-dsDNA levels progression of proteinuria improved survival</p>
IL-6 in human SLE Systemic	<p>Increased serum IL-6 levels in active lupus Higher frequency of IL-6 secreting PBMCs Increased IL-6 production by T and B cells Increased expression of IL-6R on low density B cells in active lupus Blocking IL-6 decreased spontaneous Ig and dsDNA production <i>ex vivo</i> Effect on regulatory T cells unclear – may be different on various subsets Anti-dsDNA antibodies upregulate IL-6 production by endothelial cells and resting mononuclear cells and in turn IL-6 increases the production of dsDNA antibodies</p>
Effects on kidney	<p>IL-6 increases mesangial cell proliferation Important in related immune mediated glomerulonephritides Increased IL-6 expression in the kidneys in lupus nephritis Increased urinary IL-6 levels during active lupus nephritis</p>