# REVIEW

# Cytokines and systemic lupus erythematosus

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**Systemic lupus erythematosus (SLE)**
SLE is an autoimmune rheumatic disease that principally affects women in the childbearing years.[1] The prevalence of SLE varies between ethnic groups, being approximately 1:250 among black women, 1:1000 in Chinese women and 1:4300 in white women. SLE affects the joints, skin and blood in over 80% of patients and the kidneys, central nervous system and cardiopulmonary system in 30%–50% of patients. Between 10% and 30% of patients have anticardiolipin antibodies that are associated with arterial and venous thrombosis. The majority of patients demonstrate systemic manifestations, which may include fatigue, malaise, fever, anorexia, nausea and weight loss.

Many cytokines have been implicated in regulating disease activity and in the involvement of different organs in patients with SLE. This article reviews both the role of individual cytokines and discusses possible mechanisms of cytokine action in individual organs.

**Are cytokines important in SLE?**
Cytokine production in patients with SLE differs from both healthy controls and patients with other diseases such as rheumatoid arthritis (RA). It is important to note that cytokine production is not only changed in patients with SLE when compared with healthy controls but also changes with different disease phenotypes. For example, interleukin 6 (IL6) seems to be increased in the cerebrospinal fluid (CSF) of patients with central nervous system (CNS) involvement in SLE but not in patients with SLE who lack neurological symptoms.[2] It may be that as in other inflammatory diseases, the balance of cytokines is more important in determining disease phenotype or severity rather than in determining disease susceptibility.

**The balance of cytokines in patients with SLE**
Human CD4+ T-helper cells (Th) cells can be divided into four different subsets defined by their cytokine profile.[3–5] Th1 cells produce IL2, interferon γ (IFNγ) and tumour necrosis factor α (TNFα), Th2 cells produce IL4, IL5, IL6, IL10 (in mice) and IL13 and Th3 cells transforming growth factor β (TGFβ), IL4 and IL10. Th0 cells can produce cytokines of all three types. The concept however is more than just a division based on cyotokine production

but also on T cell function. For example, Th1 cells increase macrophage activation while Th2 cells stimulate antibody production by B cells and upregulate humoral or allergic responses. Th3 cells are regulatory cells that can act to induce immune tolerance.

The pattern of cytokine production in different disease states is therefore often described as a Th1, Th2 or Th3 response based on the cytokines produced. Although helpful, the Th1/Th2/Th3 paradigm has limitations in terms of the classification of cytokines in that cytokines such as IL6 and IL10 are synthesised mainly by monocytes. A more helpful paradigm therefore may be the classification of cytokines according to whether they upregulate or down-regulate the inflammatory cascade or response. In many inflammatory diseases such as RA and SLE it seems that the balance between proinflammatory and anti-inflammatory cytokines determines the degree and extent of inflammation and thus can lead to major clinical effects. Every proinflammatory cytokine is counteracted by either anti-inflammatory cytokines or cytokine antagonists and therefore it is the relative concentration of a cytokine to its inhibitor or antagonist that will determine its action.

**Autoantibodies in SLE**
B cells are hyperactive in patients with SLE and produce a range of antibodies spontaneously.[1] These include both autoantibodies and antibodies directed against other exogenous antigens.[1] Patients may have circulating autoantibodies against multiple nuclear, cytoplasmic and membrane antigens, with most of these being targeted towards intracellular nucleoprotein particles. Antinuclear antibodies are present in 98% of patients, with anti-double stranded (ds) DNA antibodies being found in 50%–80% of patients.[1] Of the 30–40 autoantibodies that have been identified in the serum of patients with SLE, anti-ds DNA antibodies are those thought most likely to be truly pathogenic (reviewed Morrow *et al*[1]). In vivo studies have also suggested that factors apart from naked DNA are required to produce anti-ds DNA antibodies, as mice injected with naked DNA do not develop lupus.[6] There is growing evidence to support the notion that the nucleosome is the key nuclear autoantigen in SLE.[7] High titres of high affinity IgG anti-ds DNA antibodies are virtually exclusive to SLE and are strongly associated with renal and

cardiovascular/respiratory disease.[1] T cell help necessary for antibody production is mediated via cytokines. Therefore, when tolerance breaks down and autoantibodies are produced, it would seem likely that cytokines have a part to play in the process.

### Could cytokines be involved in the breakdown of tolerance that leads to the production of α-ds DNA antibodies?

It is thought that components of the acute phase response (C reactive protein (CRP) and serum amyloid protein (SAP)) are involved in tolerance to apoptotic fragments. For example, SAP and CRP are thought to bind to circulating DNA and RNA respectively, rendering them non-immunogenic. The proinflammatory cytokines, IL6, IL1 and TNFα are thought to induce the release of acute phase proteins from the liver and so could promote removal of circulating autoantigens. This theory is supported by findings, which will be discussed in more detail later, that patients with SLE who produce low levels of TNFα are more likely to develop nephritis, a complication associated with the presence of anti-ds DNA antibodies.[8] Lacki *et al*[9] have shown that patients with SLE have normal levels of circulating TNFα and CRP as compared with either healthy controls or patients with RA. However, recent work[10] indicates that patients with active disease have significantly higher levels of serum TNFα and IL6 than patients with inactive disease. Emilie *et al*[11] also showed levels of IL6 and TNFα to be increased in active disease and that CRP levels were normal unless patients had synovitis, serositis or concurrent infection. It has been suggested (Pepys, personal communication and Lacki *et al*[9])that a relatively low CRP could cause mRNA to become immunogenic because under normal conditions, CRP binds to mRNA from nucleosomes rendering it both soluble and non-immunogenic. The presence of immunogenic mRNA could result in the production of anti-mRNA antibodies that can cross react with DNA.[9]

### Can cytokines change anti-ds dna antibody production?

Production of anti-ds DNA antibody in SLE increases in proportion to T cell activity during active disease.[12] This increase is in contrast with the situation found in quiescent SLE where production of IgG is related to B cell activity but unrelated to T cell activity.[13] Therefore, in active disease a T cell factor may be pathologically important in the production of anti-ds DNA antibodies.

CRP levels are normal in patients with SLE,[11] unless the patients have synovitis, serositis or concurrent infection despite the increase in IL6 and TNFα levels that occurs spontaneously in line with disease flares. This finding suggests an abnormal or "underpowered" acute phase response in lupus. TNFα and IL6 levels are raised in patients with active SLE but the ratio of TNFα to its soluble receptor (TNF-sR) is significantly lower in SLE when compared with patients with RA.

This observation suggests a relative deficiency of active TNFα in patients with SLE.

It is also possible that relatively low TNFα levels can predispose to anti-ds-DNA production as a subset of RA patients who received anti-TNFα therapy produced dsDNA antibodies after treatment (Tyrrell-Price, personal communication).

### Cytokine production in patients with SLE

The following section deals in turn with the individual cytokines studied whose production differs from normal levels in patients with SLE as compared with both normal healthy controls and with patients with autoimmune rheumatic disease other than SLE, notably RA. Although different haplotypes of TNFα, IL1α, IL6 and IL10 have been demonstrated in SLE, there is a significant body of data only for IL10 and TNFα. Consequently, the associations of polymorphisms or alleles with patients with SLE will be reviewed for these two cytokines.

### TNFα

GENETIC REGULATION OF TNFα PRODUCTION IN PATIENTS WITH SLE

Relatively low levels of TNFα production have been described in some patients with SLE.[14] In Korean patients with SLE, those that are "low" TNFα producers, as defined by PBMC TNFα production, are more likely to develop nephritis.[8] Stimulated PBMCs or enriched monocyte populations taken from both patients with SLE or healthy controls who are Dqw1 and DR2 positive, produce lower levels of TNFα than DR3 or DR4 positive subjects. There is a strong association between the MHC class 2 DR2, Dqw-1 and/or DR3 alleles and SLE. However, this association may be because of linkage disequilibrium with TNFα alleles as the TNFα gene lies within the class III region of the major histocompatibility complex about 250 kilobases centromeric of the HLA-B locus and about 850 kilobases telomeric of HLA-DR.[15] Two polymorphisms have been described in the TNFα 5' regulatory region at −308 and −238.[16 17] The rare allele at −308 is part of an extended MHC haplotype HLA-A1-B8-DR3-DQ2[18] that is associated with high TNFα production.[14 19] This has been confirmed in transfection studies in which the rare (TNF2) allele is a much more powerful transcriptional activator then the common allele.[20] Associations between patients with SLE and the rare TNF2 allele have been reported in white patients but not confirmed in other populations.[21] TNF microsatellite polymorphisms have also been investigated and associations have been described between white patients in the United Kingdom and alleles a2, b3 and d2,[22] and between allele a2 and multiplex SLE families in Sweden. In this population the TNFabc haplotype 2–3–1 was more common in SLE associated haplotypes than in non-SLE haplotypes and was associated with the extended MHC haplotype HLA-B8, SC01, DR17. Linkage disequilibrium between the TNF microsatellite alleles and HLA haplotypes in Greek patients with SLE has also been described. It is unclear whether

these associations are actually an artefact attributable to population stratification because not all associations have been confirmed in different populations. One study of patients with SLE, found that serum concentrations of TNFα were no different from normal controls but increased levels of soluble TNFα receptor correlated positively with the degree of disease activity.[23] The ratio of TNFα to the soluble TNFα receptor is crucial because the receptor acts as an inhibitor for TNFα and would therefore decrease its biological activity. It is interesting to note that, while SLE is a relatively common disease in the black populations of the West Indies and America, it is seldom seen among the black populations of sub-Saharan West Africa who have a very similar genetic background.[24] This finding implicates environmental factors in the incidence of disease but it is also possible that genetic admixture between people of African origin and other inhabitants of the Americas may have led to increased susceptibility to SLE. Detailed epidemiological studies have to be carried out but it has also been postulated that the rare occurrence of SLE in sub-Saharan Africa is associated with exposure to infection, notably malaria. Currently, the contribution of the genetic differences within the TNFα genes in patients with SLE and the possible role of environmental factors is still unclear.

ROLE OF TNFα IN THE PATHOLOGY OF SLE

Dqw1 or DR2 positive patients with SLE were more likely to suffer from nephritis than DR3 positive patients. As discussed above, these haplotypes are associated with lower TNFα production by monocytes. It therefore seems possible that a strong TNFα response is protective against lupus nephritis.

Further corroboration of the protective role of TNFα was given by measurement of plasma levels of TNFα and its soluble receptor TNF-sR2 in nine patients with active lupus nephritis and five normal controls, using an ELISA technique.[25] It was found that the nine patients all had increased levels of TNFα compared with the five healthy controls. However, the ratio of TNFα to its soluble receptor was decreased in the patients compared with the healthy controls. This could lead to a lower effective level of TNFα in the blood of patients with lupus nephritis. It would have been interesting to see the comparison of TNFα and sTNF-R2 levels in patients with SLE and both with and without nephritis.

Despite this apparent protective role of TNFα, 52% of renal biopsy samples from 19 patients with lupus nephritis have TNFα protein deposited along the glomeruli and tubules as demonstrated by immunofluorescence.[26] In situ hybridisation and RT-PCR amplification showed local expression of these cytokines in seven of the biopsy specimens (six with type IV and one with type III nephritis) indicating that they are synthesised in the kidneys of patients with nephritis. This finding implicates TNFα in the pathology of lupus nephritis but in the absence of measurements of the level of TNF-sR it is not possible to determine whether TNFα exerts a proinflammatory effect.

Brennan *et al*[27] in work carried out in the NZB/w or C3H/FeJ mouse models of SLE has shown that the dose of IL1 and TNFα given and the stage of disease activity dictate the pathogenic activity of these two cytokines. When these mice were injected three times weekly for two or four months with 2.0 µg or 0.2 µg IL1 or TNFα from two or four months of age, it was found that mice given the lower dose of either cytokine from the age of four months became ill and died more quickly than the untreated controls This effect was not reproduced if the cytokines were given when the mice were younger or at the higher dose. These data suggest that TNFα and IL1 have differential dose effects on renal disease in the mouse model and that the pathogenic activity of these cytokines is dictated by the dose and the stage of disease activity.

## TGFβ

TGFβ is produced by NK cells and has a powerful inhibitory effect on the production of IL6, IL1 and TNFα by macrophages in an in vitro system.[28] TGFβ suppresses B lymphocyte secretion of IgG via costimulation of CD8+ cells with IL2.[29 30] Both constitutive and stimulated levels of TGFβ are lower in patients with SLE and this is probably because of the high levels of IL10 that suppress TGFβ production by NK cells.[30] A negative correlation between CD2 stimulated production of TGFβ and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (a global disease activity score) score has been demonstrated.[30] Addition of TGFβ and IL2 to PBMCs from SLE patients reverses the upregulated IgG production via stimulation of CD8+ T cells.[9 30] It therefore seems that the high IgG production seen in patients with SLE is attributable, in part, to low levels of TGFβ and inadequate suppression of IgG production.

## IFNγ

The production of IFNγ by PBMCs from patients with SLE is significantly correlated with another global disease activity score, the Systemic Lupus Activity Measure (SLAM).[31 32] In vitro production of IgG by PBMCs from patients with SLE was decreased by exogenous IFNγ.[33] Funauchi *et al*[34] showed an increase in numbers of low density (activated) B cells and a decrease in high density B cell numbers in SLE as compared with controls. They showed that high density B cells from normal controls but not from SLE were inhibited in their proliferative response to IL4 by IFNγ while the response of total B cells to PHA or IL2 induced T cell factors was increased by IFNγ in both normal controls and in patients with SLE. However, if cells were treated with IFNγ, after T cell depletion, IgG production by PBMCs was increased.[35] This finding suggests that while IFNγ can induce some or all B cells to produce more antibody, the dominant effect is inhibitory and is T cell dependent and that IFNγ may be one of the factors that promotes polyclonal B cell activation in SLE.

It has been shown[36] that there is a correlation between the subclass of antinuclear antibodies and the severity of SLE. All autoantibodies found in subacute cutaneous lupus were of the IgG1 subclass while IgG2 and IgG3 autoantibodies were also found in patients with systemic disease. IFNγ is able to induce class switching to production of IgG2 and IgG3. It would have been useful in the studies considered above to determine the subclasses of IgG antinuclear antibodies produced by the patients examined to see whether IFNγ is changing the antibody profile towards production of IgG2 and IgG3 antibodies in this in vitro system or if it is amplifying the existing response.

Work with an IFNγ receptor knockout lupus prone mouse strain (BWgammaR^{-/-})has demonstrated that only 10% of homozygous knockout animals develop immune complex glomerulonephritis by 14 months of age as compared with 50% of BWgamma^{+/+} and BWgamma^{+/-} animals by eight months old.[37] This suggests that IFNγ is essential for the development of nephritis in mice and that the increase in IFNγ during disease activation may cause an increase in IgG2 and IgG3. If there is poor clearance of IgG2 and increased complement activation through IgG3, this could worsen the nephritis. Should the same mechanism operate in patients with SLE, IFNγ could be implicated in the development of lupus nephritis.

IFNγ is thought to be implicated in the skin pathology of lupus[38] see below.

## IL1
Recent studies[32] have suggested that low levels of IL1 receptor agonist (Il-1Ra) are characteristic of kidney involvement in SLE. In a study comparing eight patients with SLE glomerulonephritis (GN) and 12 SLE patients lacking renal involvement, over a period of 8–12 months, those without GN had higher levels of IL1Ra at the time of disease flare than those with GN. IL1 is also implicated in the cutaneous pathology of SLE (see later).

## IL2
When PBMCs from patients with SLE are stimulated with LPS and PHA, basal and induced levels of IL2 are significantly correlated with the clinical SLAM index.[32] High IL2 levels were detected in the sera of 50% of patients with active disease.[39] However, there are also increased levels of the soluble receptor for IL2 (sIL2) found in the sera of patients with active disease.[39] Freshly isolated B and T cells from patients with SLE express higher than normal levels of the low affinity IL2R.[40]

The stimulated release of IL2 has produced complicated results that are beginning to be understood. Linker-Israeli[40] showed an impaired IL2 release on mitogen stimulation of lupus PBMCs. This reduced production of IL2 correlated with an increased, spontaneous IgG production from lupus PBMCs. An increase in the number of active CD8+ cells in active disease was found and removal of these cells increased the mitogen stimulated release of IL2

in lupus patients but not in normal controls. Together with the data presented on TGFβ this suggests that an error in IL2 control may contribute to the over production of IgG antibodies in lupus.

## IL6
Nine patients with lupus nephritis were shown to have increased plasma concentrations of IL6 and sIL6R as compared with five normal controls.[25] The ratio of IL6/sIL6R is increased in lupus nephritis, suggesting a raised effective level of IL6 in SLE patients with lupus nephritis. In addition, both IL6 protein and mRNA have been found in 52% of kidney biopsy specimens taken from 19 patients with lupus nephritis.[26] IL6 is detectable in the urine of patients with lupus nephritis and may constitute a useful diagnostic marker.[41]

IL6 is necessary for bone marrow targeted plasma cell (CD38+, CD19+) survival and subsequent maturation.[42] It has been suggested that IL6 is involved in the autocrine route that maintains B cell hyperactivity.[43] IL6 receptor is constitutively expressed on B cells from patients with SLE, unlike in healthy controls.[43] Spontaneous production of IgG was not increased by the addition of exogenous IL6 in vitro although antibody secretion was inhibited on addition of anti-IL6.[42 43] Anti-IL6 antibody given to MRL lpr lupus prone mice to gain some insight into the cause of development of nephritis in a model system has been shown to cause a decrease in renal damage and a temporary reduction in levels of anti-dsDNA antibody production.[44]

SLE rash is often triggered by ultraviolet (UV) light. Exposure to UV light can induce cells from the monocyte/macrophage fraction of PBMCs taken from patients with SLE to produce IL6[45] suggesting that cytokine release may play a part in the exacerbation of SLE caused by photosensitivity. UV light can also cause apoptosis in vitro in a keratinocyte cell line, leading to the production of surface blebs containing nucleosomes and other typical lupus autoantibody targets such as R0 and La.[46] It has been suggested that nucleosomes could also induce IL6 production.[47] IL6 is also implicated in the development of cutaneous SLE, see later for further details.

High levels of Il6 have been shown to be implicated in the development of cardiopulmonary disease, which can take the form of pericarditis, valvular abnormalities (25%), pleural effusions, lupus pneumonitis, pulmonary hypertension and interstitial pneumonitis. Yoshio et al[48] showed that endothelial cells pretreated with IL1β suppressed the release of IL6 if they were treated with control sera or sera taken from SLE patients without cardiopulmonary involvement. However, high levels of stimulation were observed when the endothelial cells were treated with sera from five patients with pulmonary hypertension. Similar high levels were observed when purified IgG or F(ab')2 fragments from these patients were used in the assay. These results implicate IL6 in the pathogenesis of pulmonary hypertension in

SLE and suggest that IgG antiendothelial cell antibodies in SLE patients may also play a part.

## IL10

Twin studies and family studies have suggested that approximately 75% of the variation in IL10 production is genetically determined.[49] In multiplex families where there are at least two members with SLE, IL10 production by PBMCs is increased in the healthy relatives.[50] However, no such increase in IL10 production is seen in the healthy relatives when only one member of the family has SLE. This survey suggests that the genetic regulation of IL10 is important in most patients with SLE.

IL10 production seems to be controlled at the transcriptional level.[51] The IL10 5' flanking region, which controls transcription, is polymorphic with two microsatellites between −4000 and −1200[52 53] and three single base pair substitutions between −1082 and −592 bps from the TATA box. The two satellite regions have been described as G (about −1000 kb) and R (about −4000 kb). Whole blood culture suggests the presence of high and low IL10 producing haplotypes with R3G7 being the lowest IL10 producing haplotype and R2G14 having the highest IL10 production. Comparison of haplotypes within each locus suggests that G7 is low, G14 is high and R3 is low.

Associations have been described between alleles at both microsatellites and SLE. In SLE there seems to be an association with a reduction in the IL10.G 9 allele and an increase in IL10.G 13. There is a difference in allele distribution between patient subgroups using Monte Carlo simulation methodology that obviates the need for a multiple test comparison.[54] However the numbers in the subgroups are small and although the Monte Carlo simulation method allows analysis of multiple alleles without a Bonferoni correction, it does not also allow for multiple analysis of subgroups without a Bonferoni correction. The G13 allele that is increased in patients with SLE does not seem to be the allele associated with higher IL10 production.

The IL10 microsatellite at −1 Kb has also been investigated in Mexican Americans with SLE in a relatively large study involving 158 patients and 222 ethnically matched controls.[55] In this study, microsatellites were also typed for the bcl-2, Fas-L and CTLA-4 genes thought to be involved in programmed cell death. The most common allele in Mexican Americans is the 125 bp allele, which is probably equivalent to the IL10.G 9 allele (also the most common allele with a similar population frequency of 0.5) described by Eskdale *et al*.[54] In this study, associations were investigated using logistic regression analysis that showed a decrease in the 125 bp allele in patients with SLE consistent with the results from Eskdale *et al*.[54] In addition, they describe an increase in the 127bp allele in the Mexican population that was not seen in studies on a Glaswegian population. They also describe a synergistic effect between this high risk allele and the high risk bcl-2 allele and showed significant interaction with an odds ratio for both alleles of 40. As the bcl-2 and IL10 genes in the human reside on different chromosomes, this synergism is not attributable to linkage disequilibrium.

In addition to the microsatellites described, there are also three single nucleotide polymorphisms (SNPs) previously assigned to positions 1082 (G to A), −819 (C to T) and −592 (C to A) respectively.[52 56] The G to A nucleotide polymorphism occurs within a putative Ets transcription factor binding site. The C to T nucleotide polymorphism lies within a putative positive regulatory region[57] and the C to A polymorphism lies within a putative STAT 3 binding site and a negative regulatory region.[57] There is linkage disequilibrium between the alleles with the two downstream polymorphisms occurring in tandem, and only three of four possible haplotypes have been found in white populations: GCC, ACC and ATA. In patients with SLE, an association has been reported between patients with anti-Ro antibodies and the GCC or ACC haplotype[56] although the numbers studied were small and these results need confirmation from larger population association studies. An association has also been described in a southern Chinese population between patients with SLE nephritis and the ATA haplotype. However, the distribution of haplotypes in the Chinese population are so different from those described in white populations it is not clear whether this is because of ethnic differences or the different methodology used.[58] Our recent study of larger disease and control populations in the UK has failed to confirm these associations.[59]

Serum IL10 levels are higher in patients with SLE when compared with controls.[9] This increase is mainly attributable to an increase in IL10 production by monocytes, a subset of B cells and possibly CD4+CD45 RO+ memory T cells.[9 60 61] Serum titres of IL10 are positively correlated with anti-ds DNA antibody titres and the SLEDAI score and negatively correlated with complement C3 levels.[62 63] IL10 increases IgG production by PBMCs from patients with SLE.[64] In healthy controls, IL10 stimulates B cell proliferation and IgG synthesis and this is increased when the cells are activated through CD40 before stimulation.[65] Expression of CD40L on PBMCs is at the lower limit of normal in patients with inactive SLE however, T cells from patients with SLE hyperexpress CD40L during active disease and after mitogenic stimulation.[66] B cells from healthy controls will not express CD40L without extensive pharmacological manipulation[67] although B cells from patients with active disease express CD40L constitutively. However, TNFα is not thought to play a direct part in antibody production in SLE although it may cause the release of IL6, which will affect antibody secretion.[68]

One report has proposed that lymphocytes isolated from patients with SLE have an increased rate of apoptosis as compared with

normal controls and patients with RA.[69] Treatment of PBMCs from active SLE patients with neutralising anti-IL10 antibody reduces the rate of apoptosis by 50%.[70] This effect was shown to be attributable to an effect on the action of IL10 by addition of exogenous IL10 to PBMCs that decreased cell viability by 38% in PBMCs from patients with SLE but had no effect on normal controls.[70]

## IL12

IL12 production by PBMCs is lower in SLE patients than in healthy controls and this seems to be because of decreased IL12 production from monocytes.[71] IL12 production is also lower in patients with active disease when compared with those with inactive disease.[71] Treatment with recombinant anti-IL10 antibody reversed the deficiency in IL12 production by PBMCs from patients with SLE but had no effect on PBMCs from healthy controls. This finding suggests that the low IL12 production seen in patients with SLE is attributable to the excessive IL10 production that is known to occur in the disease.

## IL16

Serum concentrations of IL16 are raised in patients with SLE when compared with healthy controls and this increase seems to correlate positively with the SLEDAI score.[72]

## Cytokine involvement in the skin, kidney and neurological systems

The abnormal cytokine profile seen in patients with SLE also varies between the different phenotypes of the disease. Cytokines are generally produced by cells local to where they will have their effect. The levels of specific cytokines at the site of pathology may be characteristic of the disease while the levels found in the circulation are unaltered compared with controls. The following section considers three of the major systems of the body commonly affected in SLE and highlights the specific cytokines that may be implicated in the development of disease pathology.

## Role of cytokines in SLE skin disease

About a third of patients with SLE have cutaneous involvement that commonly takes the form of a photosensitive erythematous "butterfly" rash with malar distribution. Many patients also have alopecia.

Circulating IgG antiendothelial cell antibodies are found very commonly in patients with SLE with one study showing 38 of 41 patients with SLE to have these antibodies.[73] IL1α increases the binding activity of anti-endothelial cell IgG unlike TNFα and IFNγ that do not change binding.[73] It was found that sera from patients with joint or skin abnormalities showed increased binding to endothelial cells as compared with patients without these manifestations, regardless of whether or not the endothelial cells had been pre-stimulated with IL1α. While it may be inferred from these findings that IL1α might play a part in autoimmune

vascular damage in SLE, it would be necessary to attempt blocking studies using anti-IL1α antibodies to confirm this theory.

Cutaneous manifestations of SLE are often triggered by exposure to UV irradiation in both murine and human disease. IL1α mRNA present in the skin of lupus prone NZB mice is increased by UV irradiation as compared with controls.[74] A possible mechanism for involvement of IL1α in the skin therefore is that UV irradiation increases IL1α in the skin and this in turn increases binding of anti-endothelial IgG to endothelial cells in the skin. Study of spleen cell cultures taken from these mice also showed an increase in the number of anti-DNA antibody producing cells, which could suggest that cutaneous upregulation of IL1 may mediate the development of other manifestations of the disease. However, it needs to be shown that anti-IL1 antibodies could block the upregulatory effect before such a conclusion could be drawn.

Patients with cutaneous manifestations of lupus are more likely to have mRNA for IL2, IL4 and IL5 in skin biopsy specimens than healthy controls where mRNA for IL5, IL4 and IL2 is undetectable. These patients are less likely to have IL10 mRNA than controls in whom it is ubiquitous. From these findings, the authors inferred a role in the skin pathology of SLE for Th2 type cells and suggested that these IL5 producing cells may be involved in augmentation of disease in combination with local production of IFNγ. IL6 has been demonstrated in 14 of 26 lesional skin biopsy specimens taken from patients with various types of lupus erythematosus[75] with the immunolabelling being most intense in the basal layer of the epidermis irrespective of the LE subtype. There was minimal or no labelling in both the remaining lesional biopsy specimens and the non-lesional biopsy specimens and the normal control skin. However, of the 12 patients with SLE from whom the biopsy specimens were taken, eight had been pretreated with either local or systemic anti-inflammatory drugs that could bias the result in favour of low IL6 production. There was no correlation between immunoglobulin and complement deposition at the dermoepidermal junction and IL6 expression in keratinocytes. Therefore, although IL6 may be important in the development of dermal pathology, the exact mechanism is unknown.

## Role of cytokines in renal disease

IL6 has been found in 52% of kidney biopsy specimens taken from a total of 19 patients with lupus nephritis[26] and confirmation of the local production of IL6 along the glomeruli and tubules of seven of these patients determined by in situ hybridisation and RT-PCR.

TGFβ has been shown to decrease spontaneous IgG production in SLE[29] but levels of TGFβ are relatively low in lupus (see above)[76] and it seems that there is a cytokine imbalance in lupus renal disease with an increase in proinflammatory cytokines such as IL6 and IFNγ and a decrease in anti-inflammatory cytokines such as TGFβ.

### Role of cytokines in neurological disease

The neurological manifestations of SLE may vary from migraine, anxiety, depression or mild cognitive dysfunction in the minor forms to strokes or psychoses at the other end of the spectrum.

Alcocer-Varela *et al* showed that the cerebrospinal fluid (CSF) of SLE patients with CNS involvement had increased levels of IL1 and IL6[77] but no detectable TNFα and IL2. T cells taken from the CSF of these patients were shown to express higher levels of late and very late activation antigens (T10 and VLA-1 respectively) when compared with controls who had neurological symptoms but lacked the diagnostic markers of an inflammatory neurological disease. It was also established that neither IL1, IL6 or normal CSF were able to induce the expression of T10 or VLA-1 on normal T cells.

Gilad *et al* investigated CSF cytokine levels in two groups of young adults, one of whom had presented after a stroke and the other having neurological symptoms with no objective evidence of a neurological disease.[78] There were no differences in cytokine levels except in the levels of soluble IL2 receptor (SIL-2R). This work showed that stroke patients who went on to be diagnosed as having SLE had significantly higher levels of SIL-2R in their CSF. This study differs from the previous one in that it measures SIL-2R before the diagnosis of SLE and it is possible that at the onset of the disease this would no longer be detectable if bound to IL2. The control group had neurological symptoms and so the increase in IL1 and IL6 could be attributable to intrinsic neurological disease and not specifically attributable to SLE. This contrasts with Jara *et al*[2] who compared groups of patients with and without neurological disease and with and without SLE and showed that IL6 is increased in the CSF of SLE patients with CNS involvement as compared with the other groups and that over half of these patients had higher levels of IL6 in their CSF than in serum. Serum IL6 was found to be higher in the CNS SLE patients than in normal healthy controls and SLE controls. However, there was no difference in serum IL6 levels in the patients with neurocysticercosis compared with the SLE CNS group. This finding suggests that it is the level of IL6 found in the CSF, where it is local to the disease pathology that is characteristic of SLE with neurological manifestations rather than the levels circulating in the serum.

### Conclusion

From the data discussed the imbalance in the levels of cytokines and their receptors found in SLE is clearly crucial to the development of the pathology of the disease. Figure 1 summarises the differences in cytokine levels seen in patients with SLE compared with normal controls and it can be seen that depending on the phenotype of the disease, the cytokine profile may differ between patients with SLE. In the case of TNFα, although the level of cytokine may be raised in renal disease, the effective level is lower compared with healthy controls because the ratio of TNFα to its soluble receptor is decreased. Genetic predisposition towards production of high levels of TNFα seems to be protective against development of lupus nephritis. In contrast, IL6 is detected at high levels both locally and in the serum of patients with lupus nephritis. IL6 is also increased in the CSF of patients with neurological manifestations of SLE. In this case, it has been seen that the increased levels of circulating IL6 in the serum are characteristic of an inflammatory neurological condition rather than diagnostic



Skin disease
IL2, IL4 and IL5 mRNA in skin biopsies (undetectable in normal controls)
IL10 mRNA less frequent (ubiquitous in controls)
IL6 and IL1α increased

Systemic lupus erythematosus

Neurological disease
IL1 and IL6 increased in CSF
IL2 and TNF undetectable in CSF. Serum IL6 no different from disease controls

Renal disease
Local production of IL6 in kidney biopsies. High levels in urine. Increased in serum
IFNγ, TNFα, IL1Ra, IL4 and IL10 increased in serum
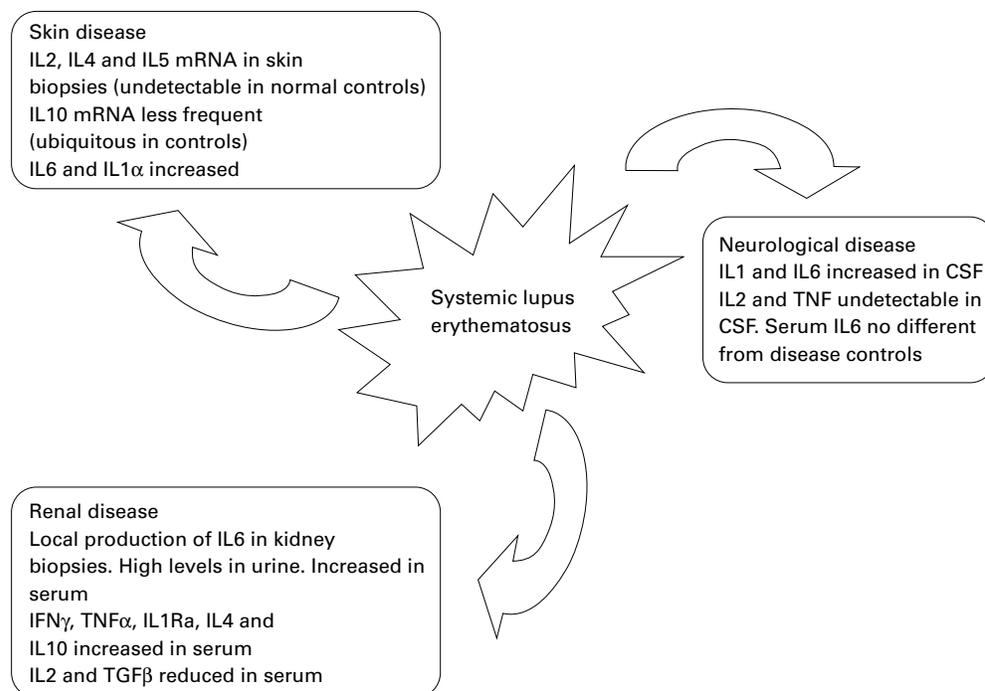IL2 and TGFβ reduced in serum

*Figure 1 Summary of abnormal cytokine profiles in skin, kidney and neurological systems.*

of the disease. This example shows the limitations of measuring serum cytokine levels as a diagnostic tool in SLE. However, the cytokine levels at the site of pathology can be very useful where they can be measured. This is not surprising because most of the cytokines are produced near their site of action and would not necessarily be released into the circulation. Cytokines interrelate in their effects on the development of the pathology of SLE and their interactions have been considered in the review. Any treatment for SLE that involved manipulation of the cytokine profile to, for example reduce the levels of IL6 or increase TNFα production would need to be approached with caution considering effects on the cytokine network as a whole.

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