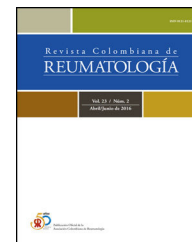




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Review Article

Role of cytokines in the pathophysiology of systemic lupus erythematosus

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ABSTRACT

The physiological mechanism in systemic lupus erythematosus is not yet fully elucidated. It is currently known that it is a multifactorial autoimmune disease which includes genetic, environmental and immune factors. Over the years it has been reported that cytokines play a predominant role during the course of the disease. In this review some findings reported in recent years were reviewed and the most important cytokines in SLE were considered; and we analyzed how the levels of each cytokine have been found in patients and how each of them can contribute to the proposed mechanisms and the relationship with the disease, as well as their possible effects on the triggering and control of systemic lupus erythematosus. The aimed of this article is to provide a focused review of the current knowledge of cytokines in SLE.

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Papel de las citocinas en la fisiopatología del lupus eritematoso sistémico

RESUMEN

Los mecanismos fisiopatológicos en el lupus eritematoso sistémico (LES) aún no están completamente elucidados. Actualmente se sabe que es una enfermedad autoinmune multifactorial que comprende factores genéticos, ambientales e inmunes. A lo largo de los años se ha reportado que las citocinas tienen un papel preponderante durante el curso de la enfermedad. En esta revisión, algunos hallazgos reportados durante los últimos años fueron revisados para algunas de las citocinas más importantes descritas en el lupus, se analizó cómo se han encontrado los niveles de cada citocina en los pacientes y cómo cada una de ellas puede contribuir a los mecanismos propuestos, también se abordó su relación con la

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enfermedad, así como sus posibles efectos en el desencadenamiento y control del LES. El propósito de este artículo es brindar una revisión focalizada en el conocimiento actual de las citocinas en el LES.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects around 5 million people worldwide.¹ Like several other autoimmune diseases, SLE affects women more frequently than men, mainly women in fertile age between 15 and 44 years old, with female to male ratios exceeding 9:1.² Despite years of study, this sex predilection and its consequences remain incompletely understood.

In Colombia, between 2012 and 2016, 431,834 cases of SLE were registered, for a prevalence of 91.9 per 100,000 inhabitants. The prevalence in women was 161.3 per 100,000 population, and in men it was 20.9 per 100,000 population, for a female: male ratio of 7.9: 1. The departments of Colombia with the highest prevalence were in their order Bogotá DC, Antioquia and Valle del Cauca.

In the city of Bogotá, 13,747 patients with this pathology were registered, being the city with the highest prevalence followed by the Antioquia region with 9893 affected.³ Cytokines play an important role during the course of the disease.⁴ In this review, some of the most important cytokines findings during the last years in SLE were addressed, it was analyzed how each cytokine can contribute to the proposed mechanisms, and its relationship with the disease, as well as its possible effects on the triggering and control of SLE. The aimed of this article is to provide a focused review of the current knowledge of cytokines in SLE.

Methods

Original and review articles were selected published in English or Spanish from 2009 to 2020 in MEDLINE/Pubmed and Science Direct (Elsevier). The following search terms were used ((Systemic lupus erythematosus [Title]) AND (Cytokines [Mesh] OR chemokines)) AND (Pathology [Mesh] OR pathophysiology)). The articles were then selected regarding the measured level of the cytokine or chemokine and the potential role in the pathophysiology mechanism proposed to SLE.

Results

In the following part, we present for each cytokines studied, a brief description of the general role of each cytokine, then how the level of the cytokine is found in SLE patients in comparison with healthy controls and finally, the possible implications in the SLE mechanism in the pathophysiology.

IFN- α

IFN- α is a cytokine that belongs to the family of type I interferons, which are glycoproteins known for their ability to interfere with viral infections. This cytokine is mainly produced by plasmacytoid dendritic cells in response to exogenous stimuli, such as bacterial and viral pathogens, as well as to endogenous stimuli, such as nucleic acids, and immune complexes containing nucleic acids that are recognized by Toll-like receptors (TLR).⁴ The multiple effects of IFN- α include activation of dendritic cells; promotion of the proliferation, survival and differentiation of monocytes into dendritic cells, and differentiation of B cells into plasma cells. In addition, it has been described that it improves the activity of natural killer cells enhancing the production of cytokines, degranulation and cytotoxic activity of these cells.⁵ It also stimulates the Th1 pathway but is not sufficient to promote the differentiation.⁶ IFN- γ as a Th1 hallmark cytokine, preventing apoptosis of activated cytotoxic T cells; and suppresses regulatory T cells.^{4,7}

IFN- α has been found increased in patients with active disease, compared to those with mild or moderate disease and healthy controls, and a positive correlation has been described between IFN- α levels and the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) suggesting that the presence of higher levels of IFN- α increase the activity in SLE patients. Studies carried out by Abdel et al., showed that IFN- α levels are increased in the group of patients with highly active disease or severe disease (measured by SLEDAI index ≥ 12), compared to the groups that had mild or moderate disease; in this study it was also pointed out that there was a positive correlation between the serum levels of this cytokine and SLEDAI in patients with lupus nephritis.⁸ Similar results were reported by Liu et al., who also found an overproduction of IFN- α in SLE compared to healthy controls and patients with rheumatoid arthritis (RA), and how it helped the production of IL-6 by transitional B lymphocytes of patients (Btr), promoting their survival. Btr is a subset of lymphocytes described as important link between immature B cells in bone marrow and mature B cells in periphery that play a regulatory role and are functional impairment in autoimmune diseases.^{9,10} A positive correlation has also been described between IFN- α levels and the presence of immune complexes in the serum of patients, as well as deposits of immune complexes in kidney sections from SLE patients. The increased IFN- α can inhibit the production of c-reactive protein (CRP) through enhancer binding proteins such as (C/EBPs) β and δ and STAT-3, leading to an increase in available autoantigens, this is because it has been reported that CRP participates in the opsonization and clearance of apoptotic cells.^{11–13} This cytokine is one of the most strongly implicated in the pathogenesis of SLE; elevated serum

levels of this cytokine have been correlated with clinical manifestations such as fever, rash, and lymphopenia.¹⁴ One of the mechanisms in which it contributes to disease development is the promotion in the maturation of antigen-presenting cells and their respective molecules necessary for antigen presentation such as MHC-I, MHC-II, and stimulating molecules.¹⁵ IFN- α can increase the expression of autoantigens such as Ro52, a well-established autoantigen, which is translocated into the nucleus promoting apoptosis and generating cell fragments¹⁶; autoantibodies capable of forming interferogenic immune complexes together with RNA-type autoantigens were also detected in cerebrospinal fluid, indicating that this cytokine also compromises the central nervous system,¹⁷ likewise the glomerular and synovial tissues, in which the accumulation of IFN- α -producing plasmacytoid dendritic cells has been reported promoting nephritis. Additionally, it can also be found in skin lesions a continuous release IFN- α leading to skin damage such as malar rash.^{18,19} Finally, it has been associated with increased autoantibody production, defective clearance of apoptotic cells (inefficient remotion of these cells) and the promotion of T-cell-dependent inflammation.²⁰ Table 1 shows the levels of this cytokine found in the studies respect to the control groups.

TNF- α

TNF- α has two active forms, a membrane-bound and a soluble form.⁷ This cytokine is produced by different cells of the immune system, including activated T lymphocytes, natural killer cells (NK), mast cells, B lymphocytes, however, its main sources are monocytes, macrophages, and activated dendritic cells.²¹ TNF- α has pro-apoptotic functions and is linked to responses related to acute inflammation.²²

In patients with SLE, contradictory results have been reported. Some studies report elevated levels of TNF- α compared to those of healthy controls,^{23,24} while others describe that there are no differences between patients and controls. Recently, Pacheco et al. reported a statistically significant increase in TNF- α in the plasma of Colombian SLE patients with lupus nephritis in comparison with patients without lupus nephritis. These results suggest the use of TNF- α as a predictor of renal involvement in SLE,²⁵ however, Gómez et al. reported that TNF- α levels were higher in patients with inactive disease, compared to patients with highly active disease and healthy controls, suggesting that overexpression of TNF- α could be a protective factor in patients with SLE.²⁶ On the other hand, Silva et al. reported that there is no statistically significant difference between SLE patients and controls, the authors stated that these results could be due to the fact that the study subjects had inactive or mild active disease.²⁷ Therefore, the reported studies suggest that the role of this cytokine is not completely clear (see Table 1).

IL-8

Interleukin-8 (IL-8) is one of the main mediators of the inflammatory response. It is secreted by various types of cells, mainly by macrophages.²⁸ It functions as a chemoattractant and as a potent angiogenic factor.^{29,30} IL-8 mediates neutrophil chemotaxis, degranulation, increases intracellular free

calcium concentration in the neutrophil, inducing a neutrophil activation characterized by a cytokine profiling. IL-8 also is implicated in the pathogenesis of several chronic inflammatory diseases.³¹⁻³³ IL-8 is a powerful pro-inflammatory chemotactic cytokine acts on a variety of cells, the most important of which is to attract and activate neutrophil aggregation in response sites to release inflammatory mediators. Neutrophil plays a significant role in the pathogenesis of SLE and neutrophils function and phenotype disorder in SLE patients may be benefited for the pathological mechanism and complications of SLE.³⁴

Multiple studies have found elevated IL-8 levels in SLE patients in comparison to healthy controls^{24,35-41} and decreased levels after the administration of rituximab (see Table 1).³⁵ Elevated levels of IL-8 in cerebrospinal fluid, CSF, have also been detected in patients with neuropsychiatric lupus, compared to those who did not present it, additionally it was elevated during the outbreak of the disease, and it decreased significantly after treatment.^{7,42-44} Eilertsen et al., showed that IL-8 increased significantly compared to patients with a diagnosis of rheumatoid arthritis.²³ The serum level of IL-8 in patients with SLE and pulmonary involvement was also significantly higher than in patients without this type of compromise.⁴⁵ IL-8 has been evaluated in other fluids such as urine and CSF, where it has also been increased and associated with lupus activity.⁴¹ Urine IL-8 levels are associated with SLE activity and lupus nephritis.⁴⁶ Sekikawa et al.⁴⁷ observed a significant positive correlation between the number of glomerular neutrophils and IL-8 expression in renal biopsy samples obtained from lupus nephritis patients. Urine IL-8 levels in the lupus nephritis group were higher than in the non-lupus nephritis group and the healthy control group, suggesting that IL-8 may reflect the degree of kidney inflammation in nephritis patients.⁴⁸ When compared with SLE patients without organ damage, SLE patients with organ damage have significantly higher concentrations of IL-8.⁴⁹

IL-8 has been found to induce neutrophil recruitment and the formation of neutrophilic extracellular traps (NETs), increasing the risk of antinuclear autoantibody production, suggesting that it plays an important role in the early stages of SLE.^{7,50} The formation of NETs in patients can produce neoepitopes that lead to loss of immune tolerance, and NETs can contribute to vasculopathy by impairing the function of endothelial cells, promoting the formation of atherosclerotic plaque.⁵¹ The disorder of apoptotic cell clearance and NETs lead to the formation of immune complexes, and then trigger a series of immune responses against their own antigens in SLE,³⁴ therefore, IL-8, as a potent preformation factor of NETs, can be involved in the pathogenesis of SLE by increasing their formation.^{52,53} IL-8 attracts neutrophils to inflammation sites, and stimulates them to secrete a series of anti-infective agents such as a wide variety of degradative enzymes (proteases, hydrolases, nucleases), plus reactive oxygen species (ROS) via an activated NADPH oxidase in combination with myeloperoxidase³⁴ to protect the body from infection. However, the excessive effect of IL-8 on neutrophils can also cause tissue damage secreting molecules that are normally retained in phagocytic vesicles following phagocytosis of pathogens, these secreted molecules can attack host tissues if they overwhelm endogenous tissue levels of

Table 1 – Cytokines in SLE.

Cytokine	Levels	Sample type	Group studied	Possible main contribution in SLE	Reference
IFN- α	Elevated	Plasma	Active SLE vs mild and moderate SLE	• Activation and proliferation of dendritic cells	72
	Elevated	Plasma	SLE vs healthy controls	• Differentiation of B cells into plasma cells	9
TNF- α	Elevated	Serum	SLE vs healthy controls	• Suppress regulatory T cells • Promotes the inflammatory response	23,24
	Equal	Serum	SLE vs healthy controls	• Pro-apoptotic functions	27
	Elevated	Serum	Inactive SLE vs active SLE	• Activates neutrophils and endothelial cells	26
IL-8	Elevated	Plasma	SLE vs SLE with NL		25
	Elevated	Serum	SLE vs healthy controls	• Attracts neutrophils, basophils, and T-cells during the inflammatory process	7,24,34,36,37,52
	Elevated	CSF	Neuropsychiatric SLE vs SLE	• Potent angiogenic factor	42-44,49,51
	Elevated	Serum	SLE vs RA	• Induce the formation of neutrophilic extracellular traps (NETs)	23
	Elevated	Urine	SLE vs healthy controls		46-49
	Elevated	Urine	SLE vs SLE with NL		46-49
IL-6	Elevated	Serum	SLE vs healthy controls	• Stimulates B cell proliferation and immunoglobulin class switching, resulting in increased antibody secretion	43,61-63
	Equal	Serum	SLE vs healthy controls		65-68
	Elevated	Urine	SLE vs healthy controls	• Antagonistic to regulatory T cells	68
IFN- γ	Elevated	Plasma	Active and inactive SLE vs healthy controls	• Activates macrophages at the site of inflammation • Promote the production of BAFF	76
	Elevated	Plasma	Severe SLE vs healthy controls	• Induces the differentiation of naive T cells into Th1 cells	77
	Decreased	Plasma	SLE vs healthy controls		63
IL-17	Elevated	Serum	SLE vs healthy controls	• Induce and mediate proinflammatory responses • Amplify the immune response by increasing the production of autoantibodies through the stimulation of B lymphocytes	7,25,43,61,91,93,94
BAFF	Elevated	Serum	SLE with NL vs SLE	• Regulates expression of B-cell-surface proteins	82,84
	Elevated	Serum	Neuropsychiatric SLE vs SLE	• Promote T cell activation, proliferation and differentiation	98
	Elevated	Serum	SLE vs healthy controls	• Increased autoantibody production	100-104
	Elevated	Urine	SLE with NL vs SLE		105
APRIL	Decreased	Serum	SLE with NL vs SLE	• Long-term survival of plasma cells	98
	Equal	Serum	Neuropsychiatric SLE vs SLE	• Induce apoptosis	98
	Elevated	Serum	SLE vs healthy controls	• B cell activation	103
	Elevated	Urine	SLE with NL vs SLE		105
IL-2	Decreased	Serum	SLE vs healthy controls	• Differentiation of T_H cell subsets (including T_H1, T_H2 and T_H17 cells) • Homeostasis of T_{Reg} cells	108-111
IL-10	Elevated	Serum	SLE vs healthy controls	• Downregulates the expression of Th1 cytokines, MHC class II antigens, and co-stimulatory molecules on macrophages • Enhances B cell survival, proliferation, and antibody production	7,43,122-125,62,93,94,116-119,121

anti-proteinases or anti-oxidants altering the properties of the plasma membrane.⁵⁰

The levels of IL-8 in CSF in patients with neuropsychiatric involvement were higher than in patients with SLE without neurological alteration, which suggested that IL-8 could change the permeability of the blood-brain barrier, and then attract B and T cells to the inflammatory site.^{49,51,54} IL-8 regulated the permeability by down-regulation of tight junction proteins by the activation of vascular endothelial growth factor receptor-2 (VEGFR2) and up-regulation of nerve growth factor (NGF).^{55,56}

IL-8 may mediate the pathogenesis of SLE through leukocyte harvesting to organs and tissues for autoimmune damage, suggesting that IL-8 may be used as a biomarker in organ-damaged SLE patients, and a local inflammation level monitoring index. IL-8 could be considered a target for intervention and a plausible therapeutic target in SLE.⁷

IL-6

IL-6 is a pleiotropic cytokine produced in response to tissue damage. This interleukin is produced by various cell types including fibroblasts, keratinocytes, mesangial cells, vascular endothelial cells, mast cells, macrophages, dendritic cells, T and B cells.³⁹ It has both pro-inflammatory and anti-inflammatory actions, and its effects on immunity depend on the context and its local concentration.^{7,57} IL-6 exerts different hematological, immunological, endocrine and metabolic actions. This interleukin is the main stimulator of the production of most acute phase proteins. In the immune system, it promotes the differentiation and maturation of T and B lymphocytes, stimulates the production of immunoglobulins by B cells, and inhibits the secretion of pro-inflammatory cytokines such as TNF- α and IL-1. In this sense, IL-6 has anti-inflammatory actions and, together with the increase in cortisol production helps to control the inflammatory response.^{58,59} This expression is strictly controlled by transcriptional and post-transcriptional mechanisms. The continuous deregulated synthesis of IL-6 has a pathological effect on chronic inflammation and autoimmunity.³⁹

In our search regarding IL-6 levels in lupus, we found heterogeneous results. Multiple studies showed significantly higher IL-6 levels in SLE patients compared to healthy controls (Table 1).^{40,43,60-64} Thanadetsuntorn et al., stated that the combination of circulating immune complexes and IL-6 strongly predicts active clinical SLE, and that it can be used to monitor lupus activity.⁶⁴ Talaat et al., showed higher levels of IL-6 in SLE patients than in controls, and IL-6 was associated with disease activity, since IL-6 levels were correlated with high levels of anti-dsDNA antibodies.⁶³ However, other studies conclude that there was no significant correlation between serum IL-6 levels and disease activity or flare-ups.⁶⁵⁻⁶⁷ Dima et al., showed that urinary, but not serum IL-6, was related to SLE activity.⁶⁸ IL-6 does not consistently correlate with SLE disease activity, this may be due in part to a relatively short half-life and circadian rhythm of IL-6.⁴¹ IL-6 and IL-8 predicted non-renal flare, the performance of these cytokines to predict active clinical SLE is superior to complement and anti-dsDNA.⁶⁹

An important role of IL-6 among the various events involved in the pathogenesis of lupus is that it promotes the differentiation of B cells into plasma cells, with the consequent secretion of immunoglobulins. Evidence suggests an important role of IL-6 in B lymphocyte hyperactivity; B lymphocytes from lupus patients spontaneously express IL-6 receptor on the cell surface.^{70,71} Reactive T cell clones from SLE patients also produce large amounts of IL-6 and thus promote B cell activation and autoantibody production.⁴ Some authors conclude that the association of IL-6 with the disease activity is not too strong to suggest it as routine measurement, and the problems with circadian variation should be overcome before being used as a biomarker,⁴¹ because IL-6 shows diurnal variation, some studies conclude the most marked effect in early morning, others studies evidence a peak in the evening, these variation should be taken into account in order to avoid confounding by time of day in studies of IL-6 in plasma or serum.⁶⁶ However, others propose it as a sensitive biomarker to assess disease activity, as well as a predictor of remission in lupus nephritis.^{72,73}

IFN- γ

IFN- γ is the only cytokine belonging to the family of type II interferons. It is secreted by macrophages, NK cells, and T lymphocytes, especially CD4 and CD8 T lymphocytes. IFN- γ activates macrophages at the site of inflammation, contributes to the cytotoxic activity of T cells, it has antiviral capabilities, and is strongly associated with Th1 responses. IFN- γ induces the differentiation of naive T cells into Th1 cells, and triggers Th1 differentiation in an autocrine manner.^{7,74} Type I and type II IFNs binding to their respective receptors activates multiple signaling pathways, especially janus kinases (JAKs) and STAT pathways, to activate the transcription of hundreds of genes within target cells. Type I and type II IFNs have a high degree of overlap in the genes they control, inducing common biological pathways.⁷⁵

As described before for TNF- α , serum IFN- γ levels also present contradictory results (see Table 1). Some studies report a significant increase in patients with active SLE compared to inactive SLE and healthy controls,^{76,77} while other studies report decreased levels in lupus patients, or similar levels compared to controls.^{63,78,79} Talaat et al., propose that this decrease can be attributed to a previously observed reduction in the frequency and number of Th1 cells in patients with SLE.⁶³

IFN- γ is a characteristic Th1 cytokine, it participates in the pathogenesis of lupus by promoting the production of BAFF, a B-cell activating factor.⁸⁰ Patients with lupus nephritis show a dominant Th1 phenotype but a decrease in the Th2⁸¹ response in peripheral blood and the glomerulus. This phenotype is related with the severity of the renal damage. The production of autoantibodies and the incidence of glomerulonephritis decrease by blocking the IFN- γ receptor, however, it has been reported that IFN- γ can be detected in the kidney of patients with renal manifestations.⁸² Several studies on lupus models suggest that an imbalance toward the Th1 response plays a role in accelerating the disease.⁸³ In patients with SLE, an imbalance was observed in the mechanisms that regulate Th1 and Th17 cells, with an increased frequency of Th17 cells.⁸⁴

The complex role of IFN- γ in SLE is underlined by conflicting clinical studies, which find a correlation between serum IFN- γ levels and disease activity, and a correlation between IFN- γ expression and the severity of lupus nephritis, while others show reduced levels of IFN- γ in patients with lupus nephritis.^{82,85}

IL-17

IL-17 is a type I transmembrane protein, spans the entirety of the cell membrane and may function as gateways to permit the transport of specific substances across the membrane (membrane bound form). Also exist in its soluble form.^{86,87} It is a potent pro-inflammatory cytokine produced by activated T lymphocytes, being Th17 the most important producers. These Th17 cells are a subset of CD4 T lymphocytes.⁸⁸ IL-17 recruits monocytes and neutrophils, facilitates T cell infiltration, and positively regulates adhesion molecule expressions.⁸⁹ Although naive CD4 T cells can differentiate into effector subsets, the characteristic cytokine environment of SLE patients (poor in IL-2 but rich in IL-6 and IL-21) favors Th17 expansion. This set of cytokines can stimulate B cells and trigger local inflammation and tissue injury, which are related to various phenomena in the pathophysiology of SLE.⁹⁰ IL-17 can amplify the immune response by increasing the production of autoantibodies through the stimulation of B lymphocytes. IL-17-producing cells play a crucial role in disease pathogenesis and represent an attractive therapeutic target.⁶⁹

Several studies have shown significantly elevated levels of IL-17 in patients with SLE, compared to healthy controls, showing a correlation with lupus activity which is even higher in patients with nephropathy (Table 1).^{7,25,39,43,60,61,91-94}

The ability of IL-17 to induce local inflammation (target organs: kidney, skin), and a direct response of B lymphocytes allowed to postulate its participation in SLE physiopathology. Specifically, 17A and 17F have the ability to induce tissue inflammation, through the secretion of chemokines such as monocyte chemoattractant protein-1, MCP-1, growth-related oncogenic alpha protein, IL-8, IL-9, responsible for the proliferation, maturation and recruitment of neutrophils and monocytes.⁶² IL-17 induces tissue damage by regulating positively the expression of matrix metalloproteinases, and by stimulating the dendritic cells and macrophages to increase the production of IL-1, IL-6 and TNF- α .⁹³ IL-17, in addition to acting as an inflammation mediator, it also acts as a direct regulator of B lymphocyte function; specifically, this cytokine promotes B lymphocyte survival through NF- κ B and BAFF, it also alters the deletion of autoreactive B lymphocyte clones, breaks the programmed cell death of the B lymphocyte, and favors the differentiation of the B lymphocytes into plasmatic cells. All of the above effects increase autoantibody production, formation of germinal centers, and retention of autoreactive B lymphocytes in target organs.⁹⁵ With its main role in the pathogenesis of SLE, basal serum levels of IL-17 can be used as a sensitive biomarker for disease activity, and also as predictor in remission of lupus nephritis.^{72,96} Saber et al., propose it as a valuable target for future therapeutic applications.⁹⁷

Complex APRIL/BAFF

The BAFF complex is composed of the B cell activation factor (BAFF) and a proliferation induction ligand (APRIL), which are cytokines produced by macrophages, neutrophils, dendritic cells, and B lymphocytes.⁹⁸ Both cytokines bind with different affinity to three receptors expressed on B cells: BAFF receptor, transmembrane activator and cyclophilin ligand interactor (TACI), and B cells maturation antigen (BCMA). BAFF and APRIL binds to TACI as well as BCMA which is expressed on plasmablasts and plasma cells, while BAFF-R is exclusive of BAFF.⁹⁹

Multiple studies reported an increase in the serum and urine levels of BAFF and APRIL in patients with SLE compared with the healthy controls in response to the activation of Toll-like receptors on B lymphocytes, especially through TLR9.¹⁰⁰⁻¹⁰⁵ On the other hand, in SLE patients with manifestations in the central nervous system there is evidence of an increase of BAFF without a difference in APRIL; other studies with patients with renal failure found an increase of these two cytokines in urine samples but an increase in BAFF and a decrease in APRIL in the blood, these results suggest that this decrease in APRIL could be due to its renal excretion when glomerulonephritis occurs. The role of the BAFF complex in SLE is based on the importance of this cytokine in the maturation, selection, and survival of B lymphocytes and self-reactive plasma cells, and the change of immunoglobulin class isotype.¹⁰⁶ This has been tested within animal models that overexpress BAFF where a high number of B cells and autoantibodies leads to autoimmune diseases similar to lupus.¹⁰⁷

IL-2

IL-2 is a cytokine that exhibits an impressive number of different functions, it is pivotal for cellular activation, important for primary T-cell responses and essential for secondary T-cell responses.¹⁰⁸ In addition, IL-2 has the key function of down-regulating immune responses. The IL-2 production by T cells is part of a complex network in which a discrete alteration is capable of disrupting the whole system.¹⁰⁹

In the 1980s, studies showed that expression of the IL-2 receptor was increased in B cells from patients with active SLE compared with those from healthy controls, and expression of the receptor correlated with disease activity, suggesting a pathogenetic role for the IL-2 pathway in SLE. The IL-2 pathway was also discovered to be deficient in the T cells of patients with SLE, often resulting in fewer regulatory T cells compared with healthy controls.¹¹⁰

It has been reported that production of IL-2 is decreased in patients with SLE and this defect affects multiple aspects of host immunity.¹¹¹ Why do SLE T cells produce less IL-2? The decreased IL-2 production observed in SLE patients is based on the relationship between the transcription factors CRE (cAMP response element)-binding protein (CREB) and CRE-modulator (CREM). These two transcription factors share a binding of the IL-2 promoter and are responsible for activating or repressing IL-2 production. CREB occupies the binding site in resting T cells and upon activation, it is phosphorylated (pCREB) thereby promoting IL-2 transcription. IL-2 transcription is repressed by the replacement of pCREB by phosphorylated CREM (pCREM).

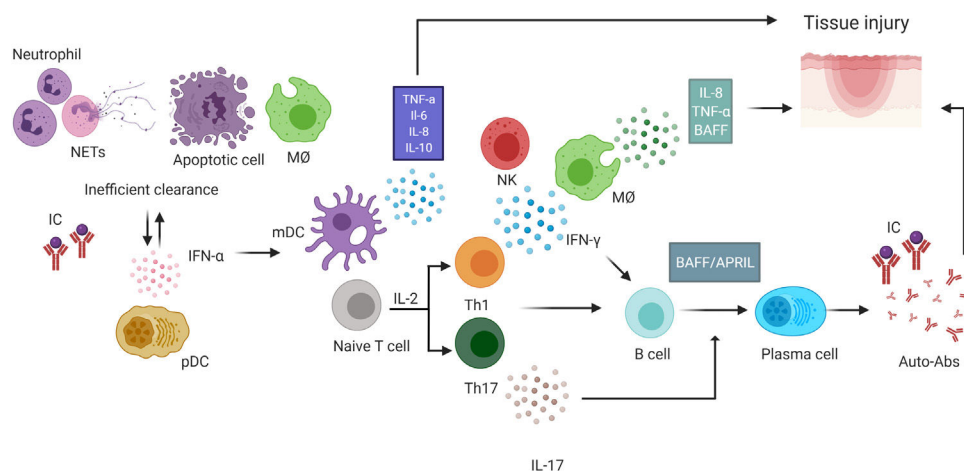


Fig. 1 – Role of cytokines in the pathophysiology of systemic lupus erythematosus (SLE). SLE is characterized by a global loss of tolerance with activation of cells of innate and adaptive immunity. In SLE, failure to effectively remove apoptotic cells by the macrophages leads an inflammatory environment and neutrophils that form NETs and undergo the NETosis, a process that also contributes to the inflammatory environment. Both processes also increase the availability of autoantigens. The antigen-presenting cell after capture autoantigens and process them to induce the activation and polarization of naïve T cells toward a Th1 profile, the predominant producer of IFN- γ that contributes to the production of BAFF and Th17 T cells, producers of IL-17. In addition to the presence of T cells, autoreactive B cells activated with the help of BAFF and APRIL produce cytokines such as IL-6, IL-8 and IL-10 and differentiate into autoantibody-producing plasma cells with the help of these cytokines and IL-17. Autoantibodies promotes tissue damage by the formation of IC. Activation of pDC by these ICs increases IFN- α production. Both mDC and macrophages produce cytokines such as TNF- α , IL-8, IL-6, and IL-10 among others. IL-8 contributes to the recruitment of neutrophils that form NETs and leads to perpetuation of the inflammatory environment. IC: immune complexes, NK: natural killer, BAFF: B-cell activation factor, pDC: plasma dendritic cell, NETs: extracellular neutrophil traps, MØ: macrophage. mDC: myeloid dendritic cells. This figure was created with Biorender.com.

SLE patients have higher levels of CREM than CREB, resulting in decreased IL-2 production.

In some strains of mice that develop an SLE-like disease, treatment with low-dose IL-2 prolonged survival, resolved nephritis, and reduced lymphadenopathy.¹¹⁰

In vivo low-dose IL-2 administration in humans has been confirmed to be safe and effective in expanding Treg,¹¹⁰ it is likely that it may be considered for the treatment of several autoimmune diseases including SLE. Low-dose IL-2 significantly expands regulatory T cells, expansion of regulatory T cells while suppressing inflammation is an attractive approach to management of patients with SLE. Several clinical trials have explored the use of low-dose IL-2 in patients with SLE,^{69,112} showing that low-dose IL-2 therapy is safe and well tolerated and selectively promotes the expansion of functional regulatory T cells in patients with moderate-to-severe systemic lupus erythematosus.

IL-10

Interleukin-10 is a homodimeric protein produced by macrophages, dendritic cells, and helper T cells in response to multiple stimuli.⁷³ It decreases the activation of antigen-presenting cells, negatively regulates the expression of costimulatory molecules, and reduces the activation of T cells and the secretion of TNF- α .¹¹³ IL-10 plays a crucial role in inflammatory and immune reactions. It has potent anti-inflammatory and immunosuppressive activities on myeloid cell functions which forms a solid basis for its use in acute

and chronic inflammatory diseases.¹¹⁴ The anti-inflammatory and tolerogenic cytokine IL-10 appears to play a paradoxical pathogenic role in SLE and is therefore currently therapeutically targeted in clinical trials. It is generally assumed that the pathogenic effect of IL-10 in SLE is due to its growth and differentiation factor activity on autoreactive B-cells, but effects on other cells might also play a role.¹¹⁵

Multiple studies have shown that serum IL-10 is increased in SLE patients compared to controls (see Table 1).^{25,39,43,62,92-94,116-126} IL-10 levels were positively correlated with disease activity and anti-dsDNA antibody presence. The association observed between IL-10 and disease activity measured by SLEDAI index is supported by the correlations seen between IL-10 and other markers of disease severity included to measure the SLE activity, such as active renal disease and patients' ESR increase, C3 and C4 decrease.⁷³

IL-10 stimulates B cell proliferation and immunoglobulin class switching, resulting in increased antibody secretion with the ability to enter the extravascular compartments and promote inflammation in SLE. Various stimuli, including anti-dsDNA antibodies altering the mononuclear cell function and immune complexes by a dependent Fc γ IR mechanism are potent triggers for IL-10.^{127,128}

The ability of IL-10 to enhance B cell survival, proliferation, differentiation, and antibody production, as well as to inhibit apoptosis of autoreactive B cells, may contribute to elevated anti-dsDNA titers in SLE patients.¹²⁸ It has been shown that circulating immune complexes increase the synthesis of IL-10,

and this IL-10 can facilitate the production of autoantibodies; it could be suggested that IL-10 acts pathogenetically in SLE, amplifying and perpetuating the inflammatory cycle.¹²⁹⁻¹³¹ Several studies suggest that high concentrations of IL-10 could be used as a new biomarker to evaluate clinical activity in SLE.^{73,88,132}

Conclusion

Currently, the most important problem in the treatment of SLE is preventing and treating organ damage. Alterations in the balance between inflammatory mediators and regulators may be targets of new immunotherapeutic agents for the management of autoimmune diseases.⁴³ Cytokines play a preponderant role in pathophysiology, and may be useful to monitor the activity and severity of the disease, since many of them have been associated with this condition (Fig. 1). The use of cytokines as biomarkers is a current challenge, and perhaps the most successful strategy for their use as a biomarker is the combination of several of them, and not just one. A cytokine profile including IFN- α , IL-10, IL-8, BAFF and IL-17 could be considered as a group of cytokines to be evaluated simultaneously due to the consistent reported results across reviewed studies. The contradictory results described seem to be given by the different measurement techniques, the type of sample where the measurements are made, and the specific characteristics of the population of SLE patients studied like disease activity score. Further studies are required to deepen the understanding of the cellular and molecular mechanisms that trigger cytokines in SLE, to widen the range of therapeutic targets as potential treatments in the disease.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary material

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REFERENCES

1. Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. *Rheumatology (Oxford)*. 2017;56:1945-61, [http://dx.doi.org/10.1093/rheumatology/kex260](https://doi.org/10.1093/rheumatology/kex260).
2. Nusbaum JS, Mirza I, Shum J, Freilich RW, Cohen RE, Pillingner MH, et al. Sex differences in systemic lupus erythematosus: epidemiology, clinical considerations, and disease pathogenesis. *Mayo Clin Proc*. 2020;95:384-94, [http://dx.doi.org/10.1016/j.mayocp.2019.09.012](https://doi.org/10.1016/j.mayocp.2019.09.012).
3. Fernández-Ávila DG, Bernal-Macías S, Rincón-Riaño DN, Gutiérrez Dávila JM, Rosselli D. Prevalence of systemic lupus erythematosus in Colombia: data from the national health registry 2012-2016. *Lupus*. 2019;28:1273-8, [http://dx.doi.org/10.1177/0961203319864168](https://doi.org/10.1177/0961203319864168).
4. Jacob N, Stohl W. Cytokine disturbances in systemic lupus erythematosus. *Arthritis Res Ther*. 2011;13:1-11, [http://dx.doi.org/10.1186/ar3349](https://doi.org/10.1186/ar3349).
5. Kwaa AKR, Talana CAG, Blankson JN. Interferon alpha enhances nk cell function and the suppressive capacity of HIV-specific cd8-t cells. *J Virol*. 2019;93:1-14, [http://dx.doi.org/10.1128/JVI.01541-18](https://doi.org/10.1128/JVI.01541-18).
6. Ramos HJ, Davis AM, George TC, Farrar JD. IFN- α is not sufficient to drive Th1 development due to lack of stable T-bet expression. *J Immunol*. 2007;179:3792-803, [http://dx.doi.org/10.4049/jimmunol.179.6.3792](https://doi.org/10.4049/jimmunol.179.6.3792).
7. Rojas M, Rodríguez Y, León KJ, Pacheco Y, Acosta-Ampudia Y, Monsalve DM, et al. Cytokines and inflammatory mediators in systemic lupus erythematosus. *EMJ Rheumatol*. 2018;5:83-92.
8. Abdel Galil SM, El-Shafey AM, Abdul-Maksoud RS, El-Boshy M. Interferon alpha gene expression and serum level association with low vitamin D levels in Egyptian female patients with systemic lupus erythematosus. *Lupus*. 2018;27:199-209, [http://dx.doi.org/10.1177/0961203317716321](https://doi.org/10.1177/0961203317716321).
9. Liu M, Guo Q, Wu C, Sterlin D, Goswami S, Zhang Y, et al. Type I interferons promote the survival and proinflammatory properties of transitional B cells in systemic lupus erythematosus patients. *Cell Mol Immunol*. 2019;16:367-79, [http://dx.doi.org/10.1038/s41423-018-0010-6](https://doi.org/10.1038/s41423-018-0010-6).
10. Zhou Y, Zhang Y, Han J, Yang M, Zhu J, Jin T. Transitional B cells involved in autoimmunity and their impact on neuroimmunological diseases. *J Transl Med*. 2020;18:1-12, [http://dx.doi.org/10.1186/s12967-020-02289-w](https://doi.org/10.1186/s12967-020-02289-w).
11. Meyer O. Anti-CRP antibodies in systemic lupus erythematosus. *Joint Bone Spine*. 2010;77:384-9, [http://dx.doi.org/10.1016/j.jbspin.2010.04.010](https://doi.org/10.1016/j.jbspin.2010.04.010).
12. Ytterberg SR, Schnitzer TJ. Serum interferon levels in patients with systemic lupus erythematosus. *Arthritis Rheum*. 1982;25:401-6, [http://dx.doi.org/10.1002/art.1780250407](https://doi.org/10.1002/art.1780250407).
13. Sjöwall C, Bengtsson AA, Sturfelt G, Skogh T. Serum levels of autoantibodies against monomeric C-reactive protein are correlated with disease activity in systemic lupus erythematosus. *Arthritis Res Ther*. 2004;6:87-94, [http://dx.doi.org/10.1186/ar1032](https://doi.org/10.1186/ar1032).
14. Davis LS, Hutcheson J, Mohan C. The role of cytokines in the pathogenesis and treatment of systemic lupus erythematosus. *J Interf Cytokine Res*. 2011;31:781-9, [http://dx.doi.org/10.1089/jir.2011.0047](https://doi.org/10.1089/jir.2011.0047).
15. Crispín JC, Kyttaris VC, Terhorst C, Tsokos GCT. cells as therapeutic targets in SLE. *Nat Rev Rheumatol*. 2010;6:317-25, [http://dx.doi.org/10.1038/nrrheum.2010.60](https://doi.org/10.1038/nrrheum.2010.60).
16. Yang J, Chu Y, Yang X, Gao D, Zhu L, Yang X, et al. Th17 and natural treg cell population dynamics in systemic lupus erythematosus. *Arthritis Rheum*. 2009;60:1472-83, [http://dx.doi.org/10.1002/art.24499](https://doi.org/10.1002/art.24499).
17. Santer DM, Yoshio T, Minota S, Möller T, Elkon KB. Potent induction of IFN- α and chemokines by autoantibodies in the cerebrospinal fluid of patients with neuropsychiatric lupus. *J*

- Immunol. 2009;182:1192-201, <http://dx.doi.org/10.4049/jimmunol.182.2.1192>.
18. Tucci M, Quatraro C, Lombardi L, Pellegrino C, Dammacco F, Silvestris F. Glomerular accumulation of plasmacytoid dendritic cells in active lupus nephritis: role of interleukin-18. *Arthritis Rheum*. 2008;58:251-62, <http://dx.doi.org/10.1002/art.23186>.
 19. Farkas L, Beiske K, Lund-Johansen F, Brandtzaeg P, Jahnsen FL. Plasmacytoid dendritic cells (natural interferon- α/β -producing cells) accumulate in cutaneous lupus erythematosus lesions. *Am J Pathol*. 2001;159:237-43, [http://dx.doi.org/10.1016/s0002-9440\(10\)61689-6](http://dx.doi.org/10.1016/s0002-9440(10)61689-6).
 20. Pascual V, Farkas L, Banchereau J. Systemic lupus erythematosus: all roads lead to type I interferons. *Curr Opin Immunol*. 2006;18:676-82, <http://dx.doi.org/10.1016/j.coi.2006.09.014>.
 21. Feldmann M, Maini RN. Anti-TNF α therapy of rheumatoid arthritis: what have we learned? *Annu Rev Immunol*. 2001;19:163-96, <http://dx.doi.org/10.1146/annurev.immunol.19.1.163>.
 22. Niewold TB, Clark DN, Salloum R, Poole BD. Interferon alpha in systemic lupus erythematosus. *J Biomed Biotechnol*. 2010;2010:948364, <http://dx.doi.org/10.1155/2010/948364>.
 23. Eilertsen G, Nikolaisen C, Becker-Merok A, Nossent JC. Interleukin-6 promotes arthritis and joint deformation in patients with systemic lupus erythematosus. *Lupus*. 2011;20:607-13, <http://dx.doi.org/10.1177/0961203310392432>.
 24. Avramescu C, Biciuşcă V, Dăianu T, Turculeanu A, Bălăsoiu M, Popescu SN, et al. Cytokine panel and histopathological aspects in the systemic lupus erythematosus. *Rom J Morphol Embryol*. 2010;51:633-40.
 25. Pacheco-Lugo L, Sáenz-García J, Navarro Quiroz E, González Torres H, Fang L, Díaz-Olmos Y, et al. Plasma cytokines as potential biomarkers of kidney damage in patients with systemic lupus erythematosus. *Lupus*. 2019;28:34-43, <http://dx.doi.org/10.1177/0961203318812679>.
 26. Gómez D, Correa PA, Gómez LM, Cadena J, Molina JF, Anaya JM. Th1/Th2 cytokines in patients with systemic lupus erythematosus: is tumor necrosis factor (protective? *Semin Arthritis Rheum*. 2004;33:404-13, <http://dx.doi.org/10.1016/j.semarthrit.2003.11.002>.
 27. Da Silva AE, Dos Reis-Neto ET, Da Silva NP, Sato EI. The effect of acute physical exercise on cytokine levels in patients with systemic lupus erythematosus. *Lupus*. 2013;22:1479-83, <http://dx.doi.org/10.1177/0961203313508832>.
 28. Mohan T, Zhu W, Wang Y, Wang BZ. Applications of chemokines as adjuvants for vaccine immunotherapy. *Immunobiology*. 2018;223:477-85, <http://dx.doi.org/10.1016/j.imbio.2017.12.001>.
 29. Bishara N. The use of biomarkers for detection of early- and late-onset neonatal sepsis. In: Ohls Robin K, Maheshwari A, editors. *Hematology, immunology and infectious disease: neonatology questions and controversies*. 2nd ed. Elsevier; 2012. p. 303-15.
 30. Russo RC, Garcia CC, Teixeira MM, Amaral FA. The CXCL8/IL-8 chemokine family its receptors in inflammatory diseases. *Expert Rev Clin Immunol*. 2014;10:593-619, <http://dx.doi.org/10.1586/1744666X.89482014.86>.
 31. Sung HJ, Choi S, Lee JW, Ok CY, Bae YS, Kim YH, et al. Inhibition of human neutrophil activity by an RNA aptamer bound to interleukin-8. *Biomaterials*. 2014;35:578-89, <http://dx.doi.org/10.1016/j.biomaterials.2013.09.107>.
 32. Zeilhofer HU, Schorr W. Role of interleukin-8 in neutrophil signaling. *Curr Opin Hematol*. 2000;7:178-82, <http://dx.doi.org/10.1097/00062752-200005000-00009>.
 33. Birmingham DJ, Irshaid F, Nagaraja HN, Zou X, Tsao BP, Wu H, et al. The complex nature of serum C3 and C4 as biomarkers of lupus renal flare. *Lupus*. 2010;19:1272-80, <http://dx.doi.org/10.1177/0961203310371154>.
 34. Mao YM, Zhao CN, Liu LN, Wu Q, Dan YL, Wang DG, et al. Increased circulating interleukin-8 levels in systemic lupus erythematosus patients: a meta-analysis. *Biomark Med*. 2018;12:1291-302, <http://dx.doi.org/10.2217/bmm-2018-0217>.
 35. Barahona Correa JE, Franco Cortés MA, Ángel Uribe J, Rodríguez Camacho LS. Comparison of plasma cytokine levels before and after treatment with rituximab in patients with rheumatoid arthritis and systemic lupus erythematosus-associated polyautoimmunity. *Univ Méd*. 2018;59:1-16, <http://dx.doi.org/10.11144/Javeriana.umed59-3.cyto>.
 36. Rodríguez-Carrio J, Prado C, de Paz B, López P, Gómez J, Alperi-López M, et al. Circulating endothelial cells and their progenitors in systemic lupus erythematosus and early rheumatoid arthritis patients. *Rheumatology (Oxford)*. 2012;51:1775-84, <http://dx.doi.org/10.1093/rheumatology/kes152>.
 37. Guo R, Tu Y, Xie S, Liu XS, Song Y, Wang S, et al. A role for receptor-interacting protein kinase-1 in neutrophil extracellular trap formation in patients with systemic lupus erythematosus: a preliminary study. *Cell Physiol Biochem*. 2018;45:2317-28, <http://dx.doi.org/10.1159/000488179>.
 38. Yuan S, Tang C, Chen D, Li F, Huang M, Ye J, et al. miR-98 modulates cytokine production from human PBMCs in systemic lupus erythematosus by targeting IL-6 mRNA. *J Immunol Res*. 2019;2019:9827574, <http://dx.doi.org/10.1155/2019/9827574>.
 39. Tanaka A, Ito T, Kibata K, Inagaki-Katashiba N, Amuro H, Nishizawa T, et al. Serum high-mobility group box 1 is correlated with interferon- α and may predict disease activity in patients with systemic lupus erythematosus. *Lupus*. 2019;28:1120-7, <http://dx.doi.org/10.1177/0961203319862865>.
 40. Monzavi SM, Alirezai A, Shariati-Sarabi Z, Tavakol Afshari J, Mahmoudi M, Dormanesh B, et al. Efficacy analysis of hydroxychloroquine therapy in systemic lupus erythematosus: a study on disease activity and immunological biomarkers. *Inflammopharmacology*. 2018;26:1175-82, <http://dx.doi.org/10.1007/s10787-018-0512-y>.
 41. Aringer M. Inflammatory markers in systemic lupus erythematosus. *J Autoimmun*. 2020;110:102374, <http://dx.doi.org/10.1016/j.jaut.2019.102374>.
 42. Lu XY, Zhu CQ, Qian J, Chen XX, Ye S, Gu YY. Intrathecal cytokine and chemokine profiling in neuropsychiatric lupus or lupus complicated with central nervous system infection. *Lupus*. 2010;19:689-95, <http://dx.doi.org/10.1177/0961203309357061>.
 43. Yao Y, Wang JB, Xin MM, Li H, Liu B, Wang LL, et al. Balance between inflammatory and regulatory cytokines in systemic lupus erythematosus. *Genet Mol Res*. 2016;15:1-8, <http://dx.doi.org/10.4238/gmr.15027626>.
 44. Yoshio T, Okamoto H, Kurasawa K, Dei Y, Hirohata S, Minota S. IL-6, IL-8, IP-10 MCP-1 and G-CSF are significantly increased in cerebrospinal fluid but not in sera of patients with central neuropsychiatric lupus erythematosus. *Lupus*. 2016;25:997-1003, <http://dx.doi.org/10.1177/0961203316629556>.
 45. Al-Mutairi S, Al-Awadhi A, Raghupathy R, Al-Khawari H, Sada P, Al-Herz A, Rawoot P. Lupus patients with pulmonary involvement have a pro-inflammatory cytokines profile. *Rheumatol Int*. 2007;27:621-3630, <http://dx.doi.org/10.1007/s00296-006-0268-3>.
 46. El-Shehaby A, Darweesh H, El-Khatib M, Momtaz M, Marzouk S, El-Shaarawy N, et al. Correlations of urinary biomarkers TNF-like weak inducer of apoptosis (Tweak), osteoprotegerin (OPG), monocyte chemoattractant protein-1 (MCP-1), and IL-8 with lupus nephritis. *J Clin Immunol*. 2011;31:848-56, <http://dx.doi.org/10.1007/s10875-011-9555-1>.

47. Sekikawa T, Kashihara N, Maruyama K, Satoh M, Okamoto K, Kanao K, et al. Expression of interleukin-8 in human glomerulonephritis. *Res Commun Mol Pathol Pharmacol*. 1998;99:217-24.
48. Tsai CY, Wu TH, Yu CL, Lu JY, Tsai YY. Increased excretions of β 2-microglobulin IL-6, and IL-8 and decreased excretion of Tamm-Horsfall glycoprotein in urine of patients with active lupus nephritis. *Nephron*. 2000;85:207-14, <http://dx.doi.org/10.1159/000045663>.
49. Petrackova A, Smrzova A, Gajdos P, Schubertova M, Schneiderova P, Kromer P, et al. Serum protein pattern associated with organ damage and lupus nephritis in systemic lupus erythematosus revealed by PEA immunoassay. *Clin Proteomics*. 2017;14:32, <http://dx.doi.org/10.1186/s12014-017-9167-8>.
50. Thieblemont N, Wright HL, Edwards SW, Witko-Sarsat V. Human neutrophils in auto-immunity. *Semin Immunol*. 2016;28:159-73, <http://dx.doi.org/10.1016/j.smim.2016.03.004>.
51. Mahajan A, Herrmann M, Muñoz LE. Clearance deficiency and cell death pathways: a model for the pathogenesis of SLE. *Front Immunol*. 2016;7, <http://dx.doi.org/10.3389/fimmu.2016.00035>.
52. Gonzalez-Aparicio M, Alfaro C. Influence of interleukin-8 and neutrophil extracellular trap (NET) formation in the tumor microenvironment: is there a pathogenic role? *J Immunol Res*. 2019;2019, <http://dx.doi.org/10.1155/2019/6252138>.
53. An Z, Li J, Yu J, Wang X, Gao H, Zhang W, et al. Neutrophil extracellular traps induced by IL-8 aggravate atherosclerosis via activation NF- κ B signaling in macrophages. *Cell Cycle*. 2019;18:2928-38, <http://dx.doi.org/10.1080/15384101.2019.1662678>.
54. Grayson PC, Kaplan MJ. At the bench: neutrophil extracellular traps (NETs) highlight novel aspects of innate immune system involvement in autoimmune diseases. *J Leukoc Biol*. 2016;99:253-64, <http://dx.doi.org/10.1189/jlb.5BT0615-247R>.
55. Yu H, Huang X, Ma Y, Gao M, Wang O, Gao T, et al. Interleukin-8 regulates endothelial permeability by down-regulation of tight junction but not dependent on integrins induced focal adhesions. *Int J Biol Sci*. 2013;9:966-79, <http://dx.doi.org/10.7150/ijbs.6996>.
56. Kossmann T, Stahel PF, Lenzlinger PM, Redl H, Dubs RW, Trentz O, et al. Interleukin-8 released into the cerebrospinal fluid after brain injury is associated with blood-brain barrier dysfunction and nerve growth factor production. *J Cereb Blood Flow Metab*. 1997;17:280-9, <http://dx.doi.org/10.1097/00004647-199703000-00005>.
57. Velazquez-Salinas L, Verdugo-Rodriguez A, Rodriguez LL, Borca MV. The role of interleukin 6 during viral infections. *Front Microbiol*. 2019;10:1057, <http://dx.doi.org/10.3389/fmicb.2019.01057>.
58. González-López L. Niveles altos de IL-6 asociados a efectos sistémicos y locales en la artritis reumatoide. *El Resid*. 2015;10:38-42.
59. Rose-John S, Winthrop K, Calabrese L. The role of IL-6 in host defence against infections: immunobiology and clinical implications. *Nat Rev Rheumatol*. 2017;13:399-409, <http://dx.doi.org/10.1038/nrrheum.201783>.
60. Wang D, Huang S, Yuan X, Liang J, Xu R, Yao G, et al. The regulation of the Treg/Th17 balance by mesenchymal stem cells in human systemic lupus erythematosus. *Cell Mol Immunol*. 2015;14:423-31, <http://dx.doi.org/10.1038/cmi.201589>.
61. Tang Y, Tao H, Gong Y, Chen F, Li C, Yang X. Changes of serum IL-6 IL-17, and complement in systemic lupus erythematosus patients. *J Interferon Cytokine Res*. 2019;39:410-5, <http://dx.doi.org/10.1089/jir.2018.0169>.
62. Merayo-Chalico J, Barrera-Vargas A, Juárez-Vega G, Alcocer-Varela J, Arauz A, Gómez-Martín D. Differential serum cytokine profile in patients with systemic lupus erythematosus and posterior reversible encephalopathy syndrome. *Clin Exp Immunol*. 2018;192:165-70, <http://dx.doi.org/10.1111/cei.13095>.
63. Talaat RM, Mohamed SF, Bassyouni IH, Raouf AA. Th1/Th2/Th17/Treg cytokine imbalance in systemic lupus erythematosus (SLE) patients: correlation with disease activity. *Cytokine*. 2015;72:146-53, <http://dx.doi.org/10.1016/j.cyto.2014.12.027>.
64. Thanadetsuntorn C, Ngamjanyaporn P, Setthaudom C, Hodge K, Saengpiya N, Pisitkun P. The model of circulating immune complexes and interleukin-6 improves the prediction of disease activity in systemic lupus erythematosus. *Sci Rep*. 2018;8:2620, <http://dx.doi.org/10.1038/s41598-018-20947-4>.
65. Studnicka-Benke A, Steiner G, Petera P, Smolen JS. Tumour necrosis factor alpha and its soluble receptors parallel clinical disease and autoimmune activity in systemic lupus erythematosus. *Br J Rheumatol*. 1996;35:1067-74, <http://dx.doi.org/10.1093/rheumatology/35.11.1067>.
66. Nilsson G, Lekander M, Åkerstedt T, Axelsson J, Ingre M. Diurnal variation of circulating interleukin-6 in humans: a meta-analysis. *PLOS ONE*. 2016;11:e0165799, <http://dx.doi.org/10.1371/journal.pone.0165799>.
67. Ding J, Su S, You T, Xia T, Lin X, Chen Z, et al. Serum interleukin-6 level is correlated with the disease activity of systemic lupus erythematosus: a meta-analysis. *Clinics (Sao Paulo)*. 2020;75:e1801, <http://dx.doi.org/10.6061/clinics/2020/e1801>.
68. Dima A, Jurcut C, Balanescu P, Balanescu E, Badea C, Caraiola S, et al. Clinical significance of serum and urinary interleukin-6 in systemic lupus erythematosus patients. *Egypt Rheumatol*. 2017;39:1-6.
69. Humrich JY, Riemekasten G. Low-dose interleukin-2 therapy in refractory systemic lupus erythematosus: an investigator-initiated, single-centre phase 1 and 2a clinical trial. *Lancet Rheumatol*. 2019;1:e44-54, [http://dx.doi.org/10.1016/S2665-9913\(19\)30106-7](http://dx.doi.org/10.1016/S2665-9913(19)30106-7).
70. Ripley BJ, Goncalves B, Isenberg DA, Latchman DS, Rahman A. Raised levels of interleukin 6 in systemic lupus erythematosus correlate with anaemia. *Ann Rheum Dis*. 2005;64:849-53, <http://dx.doi.org/10.1136/ard.2004.022681>.
71. El-Shafey A, Kamel L, Fikry A, Nasr M, Abdel Galil S. Serum hepcidin and interleukin-6 in systemic lupus erythematosus patients: crucial factors for correction of anemia. *Egypt Rheumatol Rehabil*. 2020;47:1-5, <http://dx.doi.org/10.1186/s43166-020-00006-5>.
72. Abdel Galil SM, Ezzeldin N, El-Boshy ME. The role of serum IL-17 and IL-6 as biomarkers of disease activity and predictors of remission in patients with lupus nephritis. *Cytokine*. 2015;76:280-7, <http://dx.doi.org/10.1016/j.cyto.2015.05.007>.
73. Godsell J, Rudloff I, Kandane-Rathnayake R, Hoi A, Nold MF, Morand EF, et al. Clinical associations of IL-10 and IL-37 in systemic lupus erythematosus. *Sci Rep*. 2016;6:1-10, <http://dx.doi.org/10.1038/srep34604>.
74. Ohl K, Tenbrock K. Inflammatory cytokines in systemic lupus erythematosus. *J Biomed Biotechnol*. 2011;2011:432595, <http://dx.doi.org/10.1155/2011/432595>.
75. Mathian A, Hie M, Cohen-Aubart F, Amoura Z. Targeting interferons in systemic lupus erythematosus: current and future prospects. *Drugs*. 2015;75:835-46, <http://dx.doi.org/10.1007/s40265-015-0394-x>.
76. Chu M, Wong CK, Cai Z, Dong J, Jiao D, Kam NW, et al. Elevated expression and pro-inflammatory activity of IL-36

- in patients with systemic lupus erythematosus. *Molecules*. 2015;20:19588–604, <http://dx.doi.org/10.3390/molecules201019588>.
77. Cai Z, Wong CK, Kam NW, Dong J, Jiao D, Chu M, et al. Aberrant expression of regulatory cytokine IL-35 in patients with systemic lupus erythematosus. *Lupus*. 2015;24:1257–66, <http://dx.doi.org/10.1177/0961203315585815>.
 78. Kleczynska W, Jakiela B, Plutecka H, Milewski M, Sanak M, Musial J. Imbalance between Th17 and regulatory T-cells in systemic lupus erythematosus. *Folia Histochem Cytobiol*. 2011;49:646–53, <http://dx.doi.org/10.5603/fhc.2011.0088>.
 79. Dolf J, Bijl M, Huitema MG, Limburg PC, Kallenberg CG, Abdulahad WH. Disturbed Th1, Th2 Th17 and T reg balance in patients with systemic lupus erythematosus. *Clin Immunol*. 2011;141:197–204, <http://dx.doi.org/10.1016/j.clim.2011.08.005>.
 80. Tahernia L, Namazi S, Rezaei N, Ziaee V. Cytokines in systemic lupus erythematosus: their role in pathogenesis of disease and possible therapeutic opportunities. *Rheumatol Res*. 2017;2:1–9, <http://dx.doi.org/10.22631/rr.2017.69997.1010>.
 81. Robak E, Sysa-Jedrzejowska A, Robak T. Cytokines in systemic lupus erythematosus. *Przegląd Lek*. 1996;53:623–6.
 82. Uhm WS, Na K, Song GW, Jung SS, Lee T, Park MH, et al. Cytokine balance in kidney tissue from lupus nephritis patients. *Rheumatology (Oxford)*. 2003;42:935–8, <http://dx.doi.org/10.1093/rheumatology/keg255>.
 83. Tucci M, Stucci S, Strippoli S, Silvestris F. Cytokine overproduction T-cell activation, and defective T-regulatory functions promote nephritis in systemic lupus erythematosus. *J Biomed Biotechnol*. 2010;2010:457146, <http://dx.doi.org/10.1155/2010/457146>.
 84. Shah K, Lee WW, Lee SH, Kim SH, Kang SW, Craft J, et al. Correction: dysregulated balance of Th17 and Th1 cells in systemic lupus erythematosus. *Arthritis Res Ther*. 2010;12:1–10, <http://dx.doi.org/10.1186/ar2964>.
 85. Min DJ, Cho ML, Cho CS, Min SY, Kim WU, Yang SY, et al. Decreased production of interleukin-12 and interferon- γ is associated with renal involvement in systemic lupus erythematosus. *Scand J Rheumatol*. 2001;30:159–63, <http://dx.doi.org/10.1080/030097401300162932>.
 86. Kolls JK, Lindén A. Interleukin-17 family members and inflammation. *Immunity*. 2004;21:467–76, <http://dx.doi.org/10.1016/j.immuni.2004.08.018>.
 87. Zhang X, Angkasekwinai P, Dong C, Tang H. Review structure and function of interleukin-17 family cytokines. *Protein Cell*. 2011;2:26–40, <http://dx.doi.org/10.1007/s13238-011-1006-5>.
 88. Yap DY, Lai KN. Cytokines and their roles in the pathogenesis of systemic lupus erythematosus: from basics to recent advances. *J Biomed Biotechnol*. 2010;2010:365083, <http://dx.doi.org/10.1155/2010/365083>.
 89. Agarwal S, Misra R, Aggarwal A. Interleukin 17 levels are increased in juvenile idiopathic arthritis synovial fluid and induce synovial fibroblasts to produce proinflammatory cytokines and matrix metalloproteinases. *J Rheumatol*. 2008;35:515–9.
 90. Rafael-Vidal C, Pérez N, Altobás I, Garcia S, Pego-Reigosa JM. Blocking il-17: a promising strategy in the treatment of systemic rheumatic diseases. *Int J Mol Sci*. 2020;21:7100, <http://dx.doi.org/10.3390/ijms21197100>.
 91. Mendonça SMS, Corrêa JD, Souza AF, Travassos DV, Calderaro DC, Rocha NP, et al. Immunological signatures in saliva of systemic lupus erythematosus patients: influence of periodontal condition salivary cytokines in SLE patients. *Clin Exp Rheumatol*. 2019;37:208–14.
 92. Willis R, Smikle M, DeCeulaer K, Romay-Penabad Z, Papalardo E, Jajoria P, et al. Clinical associations of proinflammatory cytokines, oxidative biomarkers and vitamin D levels in systemic lupus erythematosus. *Lupus*. 2017;26:1517–27, <http://dx.doi.org/10.1177/0961203317706557>.
 93. Raymond WD, Østli Eilertsen G, Nossent J. Principal component analysis reveals disconnect between regulatory cytokines and disease activity in systemic lupus erythematosus. *Cytokine*. 2019;114:67–73, <http://dx.doi.org/10.1016/j.cyto.2018.10.013>.
 94. Guimarães PM, Scavuzzi BM, Stadtlober NP, Franchi Santos LFDR, Lozovoy MAB, Iriyoda TMV, et al. Cytokines in systemic lupus erythematosus: far beyond Th1/Th2 dualism lupus: cytokine profiles. *Immunol Cell Biol*. 2017;95:824–31, <http://dx.doi.org/10.1038/icb.2017.53>.
 95. Cubides HH, Marcela Mora CK, Viviana Parra LI, Londono JP. Profile of Th17 cytokine and its role in the pathophysiology and potential use as biomarkers in the activity of systemic lupus erythematosus. *Rev Colomb Reumatol*. 2015;22:217–24, <http://dx.doi.org/10.1016/j.rcreu.2015.08.002>.
 96. Robert M, Miossec P. Interleukin-17 and lupus: enough to be a target? For which patients? *Lupus*. 2020;29:6–14, <http://dx.doi.org/10.1177/0961203319891243>.
 97. Saber NZ, Maroof SH, Soliman DA, Fathi MS. Expression of T helper 17 cells interleukin 17 in lupus nephritis patients. *Egypt Rheumatol*. 2017;39:151–7, <http://dx.doi.org/10.1016/j.ejr.201701005>.
 98. Vincent FB, Saulep-Easton D, Figgett WA, Fairfax KA, Mackay F. The BAFF/APRIL system: emerging functions beyond B cell biology and autoimmunity. *Cytokine Growth Factor Rev*. 2013;24:203–15, <http://dx.doi.org/10.1016/j.cytogfr.2013.04.003>.
 99. Schiemann B, Gommerman JL, Vora K, Cachero TG, Shulga-Morskaya S, Dobles M, et al. All use subject to JSTOR terms and conditions an essential role for BAFF in the normal development of B cells through a BCMA-Independent pathway. *Science*. 2001;293:2111–4, <http://dx.doi.org/10.1126/science.1061964>.
 100. Wang XF, uan SL, Jiang L, Zhang XL, Li SF, Guo Y, et al. Changes of serum BAFF and IL-21 levels in patients with systemic lupus erythematosus and their clinical significance. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi*. 2007;23:1041–2. Chinese.
 101. Carter LM, Isenberg DA, Ehrenstein MR. Elevated serum BAFF levels are associated with rising anti-double-stranded DNA antibody levels and disease flare following B cell depletion therapy in systemic lupus erythematosus. *Arthritis Rheum*. 2013;65:2672–9, <http://dx.doi.org/10.1002/art.38074>.
 102. Howe HS, Thong BYH, Kong KO, Chng HH, Lian TY, Chia FL, et al. Associations of B cell-activating factor (BAFF) and anti-BAFF autoantibodies with disease activity in multi-ethnic Asian systemic lupus erythematosus patients in Singapore. *Clin Exp Immunol*. 2017;189:298–303, <http://dx.doi.org/10.1111/cei.12975>.
 103. Salazar-Camarena DC, Ortiz-Lazareno PC, Cruz A, Oregon-Romero E, Machado-Contreras JR, Muñoz-Valle JF, et al. Association of BAFF, APRIL serum levels, BAFF-R TACI and BCMA expression on peripheral B-cell subsets with clinical manifestations in systemic lupus erythematosus. *Lupus*. 2016;25:582–92, <http://dx.doi.org/10.1177/0961203315608254>.
 104. Fawzy SM, Gheita TA, El-Nabarawy E, El-Demellawy HH, Shaker OG. Serum BAFF. level and its correlations with various disease parameters in patients with systemic sclerosis and systemic lupus erythematosus. *Egypt Rheumatol*. 2011;33:45–51.
 105. Phatak S, Chaurasia S, Mishra SK, Gupta R, Agrawal V, Aggarwal A, et al. Urinary B. cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL): potential

- biomarkers of active lupus nephritis. *Clin Exp Immunol.* 2017;187:376–82, <http://dx.doi.org/10.1111/cei.12894>.
106. Schneider P. The role of APRIL and BAFF in lymphocyte activation. *Curr Opin Immunol.* 2005;17:282–9, <http://dx.doi.org/10.1016/j.coi.2005.04.005>.
 107. Mackay F, Woodcock SA, Lawton P, Ambrose C, Baetscher M, Schneider P, et al. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. *J Exp Med.* 1999;190:1697–710, <http://dx.doi.org/10.1084/jem.190.11.1697>.
 108. Bachmann MF, Oxenius A. Interleukin 2: from immunostimulation to immunoregulation and back again. *EMBO Rep.* 2007;8:1142–8, <http://dx.doi.org/10.1038/sj.embor.7401099>.
 109. Crispin JC, Alcocer-Varela J. Interleukin-2 and systemic lupus erythematosus – fifteen years later. *Lupus.* 1998;7:214–22, <http://dx.doi.org/10.1191/096120398678920028>.
 110. Wallace DJ. Low-dose interleukin-2 for systemic lupus erythematosus? *Lancet Rheumatol.* 2019;1:e7–8, [http://dx.doi.org/10.1016/S2665-9913\(19\)30019-0](http://dx.doi.org/10.1016/S2665-9913(19)30019-0).
 111. Lieberman LA, Tsokos GC. The IL-2 defect in systemic lupus erythematosus disease has an expansive effect on host immunity. *J Biomed Biotechnol.* 2010;2010:740619, <http://dx.doi.org/10.1155/2010/740619>.
 112. He J, Zhang R, Shao M, Zhao X, Miao M, Chen J, et al. Efficacy and safety of low-dose IL-2 in the treatment of systemic lupus erythematosus: a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis.* 2020;79:141–9, <http://dx.doi.org/10.1136/annrheumdis-2019-215396>.
 113. Llorente L, Zou W, Levy Y, Richaud-Patin Y, Wijdenes J, Alcocer-Varela J, et al. Role of interleukin 10 in the B lymphocyte hyperactivity and autoantibody production of human systemic lupus erythematosus. *J Exp Med.* 1995;181:839–44, <http://dx.doi.org/10.1084/jem.181.3.839>.
 114. Beebe AM, Cua DJ, De Waal Malefyt R. The role of interleukin-10 in autoimmune disease: systemic lupus erythematosus (SLE) and multiple sclerosis (MS). *Cytokine Growth Factor Rev.* 2002;13:403–12, [http://dx.doi.org/10.1016/S1359-6101\(02\)00025-4](http://dx.doi.org/10.1016/S1359-6101(02)00025-4).
 115. Geginat J, Vasco M, Gerosa M, Tas SW, Pagani M, Grassi F, et al. IL-10 producing regulatory and helper T-cells in systemic lupus erythematosus. *Semin Immunol.* 2019;44:101330, <http://dx.doi.org/10.1016/j.smim.2019.101330>.
 116. Postal M, Ruocco HH, Brandão CO, Costallat LTL, Silva L, Cendes F, et al. Interferon- γ is associated with cerebral atrophy in systemic lupus erythematosus. *Neuroimmunomodulation.* 2017;24:100–5, <http://dx.doi.org/10.1159/000479319>.
 117. Hu C, Zhou J, Yang S, Li H, Wang C, Fang X, et al. Oxidative stress leads to reduction of plasmalogen serving as a novel biomarker for systemic lupus erythematosus. *Free Radic Biol Med.* 2016;101:475–81, <http://dx.doi.org/10.1016/j.freeradbiomed.2016.11.006>.
 118. Mok MY, Wu HJ, Lo Y, Lau CS. The relation of interleukin 17 (IL-17) and IL-23 to Th1/Th2 cytokines and disease activity in systemic lupus erythematosus. *J Rheumatol.* 2010;37:2046–52, <http://dx.doi.org/10.3899/jrheum.100293>.
 119. Parodis I, Åkerström E, Sjöwall C, Sohrabian A, Jönsen A, Gomez A, et al. Autoantibody and cytokine profiles during treatment with belimumab in patients with systemic lupus erythematosus. *Int J Mol Sci.* 2020;21:3463, <http://dx.doi.org/10.3390/ijms21103463>.
 120. Yang PT, Kasai H, Zhao LJ, Xiao WG, Tanabe F, Ito M. Increased CCR4 expression on circulating CD4+ T cells in ankylosing spondylitis, rheumatoid arthritis and systemic lupus erythematosus. *Clin Exp Immunol.* 2004;138:342–7, <http://dx.doi.org/10.1111/j.1365-2249.2004.02617.x>.
 121. Koenig KF, Groeschl I, Pesickova SS, Tesar V, Eisenberger U, Trendelenburg M. Serum cytokine profile in patients with active lupus nephritis. *Cytokine.* 2012;60:410–6, <http://dx.doi.org/10.1016/j.cyto.2012.07.004>.
 122. Chun HY, Chung JW, Kim HA, Yun JM, Jeon JY, Ye YM, et al. Cytokine IL-6 and IL-10 as biomarkers in systemic lupus erythematosus. *J Clin Immunol.* 2007;27:461–6, <http://dx.doi.org/10.1007/s10875-007-9104-0>.
 123. Liu TF, Jones BM. Impaired production of IL-12 in system lupus erythematosus II: IL-12 production in vitro is correlated negatively with serum IL-10, positively with serum IFN- γ and negatively with disease activity in SLE. *Cytokine.* 1998;10:148–53, <http://dx.doi.org/10.1006/cyto.1997.0269>.
 124. Selvaraja M, Abdullah M, Arip M, Chin VK, Shah A, Amin Nordin S. Elevated interleukin-25 and its association to Th2 cytokines in systemic lupus erythematosus with lupus nephritis. *PLOS ONE.* 2019;14:1–17, <http://dx.doi.org/10.1371/journal.pone.0224707>.
 125. Torell F, Eketjäll S, Idborg H, Jakobsson PJ, Gunnarsson I, Svenungsson E, et al. Cytokine profiles in autoantibody defined subgroups of systemic lupus erythematosus. *J Proteome Res.* 2019;18:1208–17, <http://dx.doi.org/10.1021/acs.jproteome.8b00811>.
 126. Lu L, Hu C, Zhao Y, He L, Zhou J, Li H, et al. Shotgun lipidomics revealed altered profiles of serum lipids in systemic lupus erythematosus closely associated with disease activity. *Biomolecules.* 2018;8, <http://dx.doi.org/10.3390/biom8040105>.
 127. Ronnelid J, Tejde A, Mathsson L, Nilsson-Ekdahl K, Nilsson B. Immune complexes from SLE sera induce IL10 production from normal peripheral blood mononuclear cells by an Fc γ RII dependent mechanism: implications for a possible vicious cycle maintaining B cell hyperactivity in SLE. *Ann Rheum Dis.* 2003;62:37–42, <http://dx.doi.org/10.1136/ard.62.1.37>.
 128. Ouyang W, Rutz S, Crellin NK, Valdez PA, Hymowitz SG. Regulation and functions of the IL-10 family of cytokines in inflammation and disease. *Annu Rev Immunol.* 2011;29:71–109, <http://dx.doi.org/10.1146/annurev-immunol-031210-101312>.
 129. McGeachy MJ, Bak-Jensen KS, Chen Y, Tato CM, Blumenschein W, McClanahan T, et al. Cua DJ. TGF- β and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain TH-17 cell-mediated pathology. *Nat Immunol.* 2007;8:1390–7, <http://dx.doi.org/10.1038/ni1539>.
 130. Boonstra A, Rajsbaum R, Holman M, Marques R, Asselin-Paturel C, Pereira JP, et al. Macrophages and myeloid dendritic cells, but not plasmacytoid dendritic cells, produce IL-10 in response to MyD88- and TRIF-dependent TLR signals, and TLR-independent signals. *J Immunol.* 2006;177:551–8, <http://dx.doi.org/10.4049/jimmunol.177.11.7551>.
 131. Xu Q, Katakura Y, Yamashita M, Fang S, Tamura T, Matsumoto SE, et al. IL-10 augments antibody production in in vitro immunized lymphocytes by inducing a Th2-type response and B cell maturation. *Biosci Biotechnol Biochem.* 2004;68:2279–84, <http://dx.doi.org/10.1271/bbb.68.2279>.
 132. Fernández Matilla M, Grau García E, Fernández-Llanio Comella N, Chalmeta Verdejo I, Ivorra Cortés J, Castellano Cuesta JA, et al. Román Ivorra JA. Increased interferon-1 α , interleukin-10 and BlyS concentrations as clinical activity biomarkers in systemic lupus erythematosus. *Med Clin (Barc).* 2019;153:225–31, <http://dx.doi.org/10.1016/j.medcli.2018.12.012>.