Revista Colombiana de
REUMATOLOGÍA
www.elsevier.es/rcreuma

Topic Review

Profile of Th17 Cytokine and Its Role in the Pathophysiology and Potential Use as Biomarkers in the Activity of Systemic Lupus Erythematosus☆

*Héctor Hernán Cubides, Claudia Marcela Mora K., Leydi Viviana Parra I., John Londono P.**

Departamento de Reumatología e Inmunología, Universidad de La Sabana, Chía, Cundinamarca, Colombia

ARTICLE INFO

Article history:
Received 1 December 2014
Accepted 11 August 2015

Keywords:
Systemic lupus erythematosus
Th17 cells
Interleukin 17 (IL-17)
Biomarker

ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease expressed in genetically predisposed individuals. The interaction of a trigger factor together with the failure of the mechanisms for handling potential reactive autoantigens leads to the development of immune complex responsible for the damage of the target organs. Elements of both innate and adaptive immunity have been implicated in the pathophysiology of the disease, but given the heterogeneity of the SLE, we still do not have a biological marker of activity of the disease with high sensitivity, specificity and predictive value. Recently, a cell population was described as lymphocytes T helper 17 (Th17), so called because of their production of Interleukin 17 (IL-17), cytokine that mediates physiological and pathophysiological processes implicated in the development of inflammatory conditions such as SLE. It has been postulated that serum IL-17 may be a biomarker that meets these parameters; however, data on this topic is still incomplete. We present a review of the ontogenetic mechanisms of Th17 lymphocytes, an explanation of its pathophysiological role in SLE and clinical studies that support and discuss the role of Th17 lymphocytes related cytokines as biomarkers of disease activity in SLE.

© 2015 Asociación Colombiana de Reumatología. Published by Elsevier España, S.L.U. All rights reserved.

☆ Please cite this article as: Cubides HH, Mora K. CM, Parra I. LV, Londono P. J. Perfil de citosinas relacionadas con linfocitos Th17: rol fisiopatológico y potencial uso como biomarcadores de actividad del lupus eritematoso sistémico. Rev Colomb Reumatol. 2015. http://dx.doi.org/10.1016/j.rcreu.2015.08.002

* Corresponding author.
E-mail addresses: john.londono@unisabana.edu.co, londonojohn@hotmail.com (J. Londono P.).

2444-4405/© 2014 Asociación Colombiana de Reumatología. Published by Elsevier España, S.L.U. All rights reserved.

Perfil de citosinas relacionadas con linfocitos Th17: rol fisiopatológico y potencial uso como biomarcadores de actividad del lupus eritematoso sistémico

Palabras clave:
Lupus eritematoso sistémico
Linfocitos Th17
Citosina 17 (IL-17)
Biomarcador

RESUMEN

El lupus eritematoso sistémico (LES) es una enfermedad autoinmune, inflamatoria, crónica, que se desarrolla en individuos genéticamente predispuestos. La interacción de un factor detonante en conjunto con la falla de los mecanismos de depuración de potenciales autoantígenos reactivos, dará lugar a la formación de complejos inmunes responsables del daño tisular de los órganos blanco. En la fisiopatología han sido implicados una variedad de elementos pertenecientes a la inmunidad innata y adaptativa. Una población celular descrita recientemente es la de linfocitos Th17, designados así por la producción de la IL-17; citosina que media procesos fisiológicos y fisiopatológicos; estos últimos responsables del desarrollo de condiciones inflamatorias como las del LES. Dada la heterogeneidad de esta enfermedad, en la actualidad no se cuenta con un biomarcador de actividad lo suficientemente sensible, específico y con un grado de predicción, que permita una confiable toma de decisiones clínicas. Con la intención de suplir dicha carencia, se ha postulado que los niveles séricos de IL-17, pueden ser un biomarcador que cumpla con dichos parámetros. Sin embargo, la información al respecto no es conclusiva. A continuación se presenta una revisión sobre los mecanismos ontogénicos de los linfocitos Th17, la argumentación de su rol fisiopatológico en LES y los estudios clínicos que apoyan y debaten el protagonismo de las citosinas relacionadas con linfocitos Th17 como biomarcadores de actividad de la enfermedad en LES.

© 2015 Asociación Colombiana de Reumatología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Methodology

Clinical trials, observational studies, original papers and topic reviews conducted in human beings and in animal models, published in English language were evaluated for this review. The MeSH terms Th17 cells, interleukin 17, IL-17, interleukin 17 producing T helper cells, IL-17 producing T cells, Th17 related cytokines, SLE and systemic lupus erythematosus, were used in order to establish the ontogenetic mechanisms of Th17 lymphocytes, their pathophysiological role in SLE and the possible participation of the cytokines related with Th17 lymphocytes as markers of disease activity in systemic lupus erythematosus (SLE). The search engines used were: Pubmed, EBSCO, LILACS-BIREME, EMBASE, ISI and Scopus.

Introduction

SLE is a chronic systemic autoimmune disease,[1] characterized by the presence of autoimmune complexes circulating and deposited in the tissues (product of a defective clearance). Such complexes acting together with effector mechanisms of innate and adaptive immunity determine the onset, maintenance and progression of the tissue inflammation, as well as the organ damage, in a variable time of evolution. These effectors will finally determine the expression of a particular phenotype of the disease according to the affected organ.[2,3]

Similarly to what happens in other autoimmune diseases, SLE is an entity of multicausal origin and it has a pathophysiological evolution step by step in which there is a loss of the capability to recognize the self and the foreign, and an imbalance between antagonistic forces: proinflammatory and anti-inflammatory. Specifically, this loss of immunological tolerance is the product of a defective interrelation between the genetics of a susceptible individual (determined by the presence of genetic polymorphism and the race-race variation) and a shoot or trigger factor usually environmental (e.g. viral or parasitic infection, UV radiation, toxins), which condition the appearance of autoantigens (e.g. neoantigens of chromatin due to a defect in DNase) that are recognized by cells of innate immunity and presented to effector cells of adaptive immunity that are responsible for the production of autoantibodies. Finally, this production of autoimmune complexes results in both acute and chronic inflammation and complement-dependent tissue damage, direct cytotoxicity, oxidative stress, increase of vascular permeability and diffusion of cytokines and effector cells to the site of injury.[3-5]

In a deeper manner, it is necessary to establish that within the tissue inflammatory process that is generated in SLE, are involved effectors of innate immunity such as the antigen presenting cells (professional: myeloid and plasmocytoid dendritic cells, and non-professional: macrophages, monocytes) and of adaptive immunity such as the T and B lymphocytes, the last ones, producers of autoantibodies and the first ones with direct effector functions mediating processes of cytotoxicity and indirect effector functions that include the production of proinflammatory cytokines and chemoattractant molecules, as well as colony stimulating factors that induce the proliferation, differentiation and survival of other cell

groups.[1,6,7] The doctors Robert Coffman and Timothy Mossman[8] managed to distinguish, in 1986, different subgroups of T cells, the foregoing based on the differential description of surface molecules, profile of cytokines and operating modes; and thus they introduced the paradigm of the Th1 and Th2 T helper cells, which has steered our knowledge on the T cell-mediated immunity since almost 20 years ago. The Th1 cells are the product of the stimulation of "naive" CD4+ cells by IFN-γ and IL-12, thereby generating a subset of T cells, mainly producers; IFN-γ as a master molecule that orchestrates the clearance of intracellular pathogens. On the other hand, the IL-4 inhibits the Th1 response and promotes the initiation of the program of differentiation of the "naïve" CD4 + cells into Th2 lymphocytes responsible for the clearance of extracellular pathogens, primarily helminths, as well as responsible for the hypersensitivity reactions.[9,10] Despite the soundness of the prior knowledge, the Th1/Th2 paradigm has been reviewed and refuted with the description of a unique lineage of CD3+/CD4+ cells that are essentially producers of IL-17 cytokine,[11,12] such lineage called Th17 lymphocytes has been implicated, due to its high proinflammatory potential, in the explanation of the mechanisms behind the clearance of extracellular microorganisms (fungi, bacteria), and also has been implicated in acute inflammatory entities such as the acute coronary syndrome,[13] and in chronic autoimmune inflammatory conditions such as multiple sclerosis,[14] rheumatoid arthritis (RA),[15] inflammatory bowel disease,[16] ankylosing spondylitis,[17] psoriatic arthritis,[18,19] and SLE.[20] Regarding the latter we will make a special emphasis starting from the explanation of the mechanisms (IL, transcription factors, stimuli and effector cells) that determine the differentiation of a "naïve" T CD4 + cell into a Th17 lymphocyte, continuing with the explanation of the pathophysiological role (types of cells bearing receptors for Th17-related cytokines) and concluding with the review of the current evidence from clinical studies that support and debate the protagonist role of the Th17-related cytokines as biomarkers of disease activity in SLE.

Differentiation of Th17 Lymphocytes

Lymphopoiesis is a finely directed process, dependent on a set of pluripotent precursor cells of the bone marrow, which respond at the nuclear level to signals coming from their surface receptors; such nuclear response involves the activation of a series of transcription factors, responsible for the proliferation and the onset of cell differentiation, evidenced by the production and expression of cell surface marker proteins (e.g. CD: cluster differentiation) accountable for the specificity of the cell populations. In the initial stages of the differentiation, the pluripotent precursor cells express on their surface the Notch proteins, which are proteins that are cleaved upon the contact with their ligand; the intracellular portion of the Notch protein moves to the nucleus where in conjunction with the transcription factor GATA-3 define that the pluripotent precursor cells are routed to form immature precursors of T cells; these immature precursors will undergo two processes: the first, proliferation in a mechanism dependent on IL-7 produced by stromal cells of the bone marrow and the thymus, and the second process has to do with the acquisition of the first chain (β chain: αβ T cell and δ chain for the γδ T cells) of the receptor of the T cell that determines the formation of a T cell pre-receptor; the acquisition of the T cell pre-receptor and subsequently the T cell receptor (T complex receptor [TCR]: formed by both chains αβ or γδ, the ζ subsidiary chains and the CD3 co-receptor) guarantees the presence of signals of survival, proliferation and continuous maturation; in turn, the acquisition step by step of each of the components of the "T cell receptor complex" serves as checkpoints to determine which cells have failed in the event of differentiation and must enter into a programmed death cell program since they can bring with them a potential of future defects in immunity.[21,22]

The T cells that acquire their TCR, will step forward on the differentiation pathway when they express in a nonspecific and concomitant manner the CD4/CD8 co-receptors and gain, therefore, the label of CD4+/CD8+ double positive cells. Then, in a process restricted by the major histocompatibility complex (MHC) they will develop into CD4+ T lymphocytes that interact exclusively with class II MHC molecules, and as CD8+ T lymphocytes (cytotoxic) that recognize only the class I MHC molecules.[21] The "naive" CD4+ T cells migrate from the bone marrow or from the thymus to the lymph nodes where they are retained, thereafter they interact with antigen presenting cells (APC) and depending on the stimulus received by them, they can differentiate into Th1 cells, Th2 cells or Th17 lymphocytes. Specifically, in what has to do with the differentiation and activation of the Th17 population, it is necessary to indicate that the entire process begins when the dendritic cells through their dectin-1 receptors recognize the fungal β-glucans or through the Toll-like receptors recognize surface antigens of Gram-negative bacteria (or in a pathological manner, autoantigens); then subsequently they phagocytize these peptide antigens, they process them and in the endoplasmic reticulum they couple them to the class II MHC molecules, which thereafter are moved to the surface of the dendritic cell where this antigen-MHC complex interacts with the TCR complex of the "naive" CD4+ cell, thus being generated from this first contact the signal for proliferation and survival of the T cell; then takes place the contact between the CD28 receptor (constitutively expressed) of the T cell and the costimulators (expressed in an inducible manner after the MHC-TCR binding) B7-1 (CD80) or B7-2 (CD86) responsible for the second signal of activation, proliferation and survival of the T cell. After that, as a consequence of the last mentioned event, the T cell in process of activation expresses the CD40L (ligand) which is coupled to the CD40R (receptor) on the surface of the APC, thus concluding this immune synapse and first step on the path of activation and differentiation into Th 17.[21-24]

The dendritic cell produces the proinflammatory cytokines IL-1β and IL-6, which in conjunction with the transforming growth factor (TGF) TGF-β (pleiotropic cytokine produced by multiple lineages of leukocytes and stromal cells) initiate the differentiation of the Th17 lymphocyte.[23] The evidence of the fundamental role of IL-6 in the differentiation is derived from experimental murine models, in which the mice with

non-coding mutation of the two genes for IL-6, acquire resistance to develop autoimmune encephalomyelitis and collagen-induced arthritis, two *in vitro* models of autoimmune disease developed from Th17 lymphocites.[25] Explicitly, the IL-6 couples to its cell membrane receptor and favors, by signals emitted through second messengers, the activation of the transcription factor STAT-3 (signal transduction and activation of transcription) which attaches to the factors RORγt, ROR-α (members of the family of retinoic acid receptors), RUNX-1, IRF-4 and acts in cooperation with them to induce the production of the cytokines related to Th17 lymphocytes.[25]

The evidence of the action of the TGF-β comes from studies that have demonstrated that the TGF-β, that *par excellence* is an anti-inflammatory cytokine, becomes pro-inflammatory when it coexists and occurs together with the IL-6, which modifies the transcriptional program of the TGF-β. It has been demonstrated in experimental models that when the CD4+ T cell is exposed to TGF-β in an exclusive environment, the latter induces the expression of the FoxP3 gene, which is the key transcription factor in the formation or regulatory T lymphocytes (inhibitors of inflammation and autoimmunity), however, in the additional presence of IL-6 the production of regulatory T cells stops and begins the generation of Th17. There have been described many mechanisms of action for the TGF-β in the differentiation of the Th17 lymphocytes: First, the TGF-β coupled to its receptors in the cell membrane stimulates a pathway of second messengers which are responsible for activating the RORγt transcription factor.[26] Second, the TGF-β exerts its action indirectly by inhibiting the signal of the Th1 and Th2 cells that normally slow down the differentiation of Th17, specifically the TGF-β inhibits the production of IFN-γ and IL-4.[23] Finally, the TGF-β stimulates the expression of the receptor for IL-23 (IL-23R), a cytokine that is essential according to experimental models.[27] The IL-23, described for the first time by Dr. Oppman,[28] is a heterodimeric cytokine (produced by cells of the myeloid lineage: dendritic cells and macrophages) made up by the P19 protein exclusive of IL-23 and the P40 protein shared with the IL-12, it seems to be that of these 2 subunits the fundamental pathophysiologic component is the P19 protein, according to experimental models of autoimmune diseases that have demonstrated that murine species lacking p19 protein show resistance to the development of autoimmunity, contrary to what happens when the absentee is the P40 protein.

t has been demonstrated that the receptor for IL-23 (IL-23R) is expressed preferentially in the mature Th17 lymphocytes (effector cells or memory cells) and that it is almost absent in the cells in the initial stages of the transition from "naive" CD4+ into Th17, thus suggesting that rather than being a differentiation inducer cytokine, IL-23 is a cytokine promoter of proliferation and survival in the Th17 lymphocytes.[22]

Annex to the foregoing, another cytokine which takes part in the development and differentiation of the Th17 lymphocytes is the IL-21; a cytokine produced by the Th17 lymphocytes, member of the family of cytokines related with IL-2 (demonstrated in the fact that the receptors for IL-21 and IL-2 have a common α unit), which acts through autocrine and paracrine signals.[29] The analyses of differentiation of Th17 lymphocytes lacking IL-21R and the assays that have tried different combinations of cytokines, which potentially expand the Th17 population, have served as a platform to demonstrate that IL-21 is necessary to propagate the differentiation of Th17 lymphocytes and have also demonstrated that the combination TGF-β + IL-21 is sufficient and necessary to produce the differentiation of "naive" CD4+ cells into Th17 lymphocytes.[30] The IL-21 is produced according to the mechanism already described, dependent on IL-6, in turn, this IL-21 indirectly promotes the maintenance of the phenotype of Th17 through the positive stimulus for the synthesis and expression of the IL-23R; the above was confirmed by experimental murine models lacking IL-21 and IL-21R which demonstrated decreased expression of IL-23R.

Functions of the Th17 Lymphocytes and Related Cytokines

IL-17: initially called type 8 antigen associated with cytotoxic T lymphocytes, was sequenced prior cloning and described in murines by Dr. Rouvie, in 1993,[31] subsequently, Drs. Fossiez and Djossou, in 1996, cloned the human counterpart and described that it is a glycoprotein of 155 amino acids product of the encoding gene located at the 2q31 level; this glycoprotein is secreted either as homodimer or heterodimer (the first, biologically more active than the second) by activated CD4+ T cells.[32] IL-17 and its receptor IL-17R are unusual and exclusive, and they do not share homologous sequences with other cytokines. The IL-17 is a family or related cytokines, consisting of 6 members with structural similarity (they contain 4 highly conserved cysteine residues), but with divergence in the peptide sequence at the N-terminal end, which allows to distinguish several members, designated by the letters A, B, C, D, E, F; the first and the last, those with greater homology, (50% peptide sequence identity) are mainly produced by Th17 lymphocytes and, in turn, they are the members directly involved in the pathophysiological development of immune-mediated inflammatory entities, while the rest are produced by other cell groups (NK cells, NKT cells, macrophages, γδ T cells, CD4-/CD8-T cells, neutrophils), some of them, such as the IL-17E are part of the Th2 response, while the rest of their functions are still pending to be characterized.[22,23,33] All biological processes induced by the members of the IL-17 family are exerted through the receptors for IL-17 (IL-17R) which are a family of 5 members of cell surface proteins, with unique structural characteristics that differentiate them from other receptors. Designated by the letters A, B, C, D, E; of which the most important are IL-17RA (the first member described) and IL-17RC, which are capable to form by combination a functional heterodimer on which the IL-17A and F will be attached; as a group, the IL-17R exert their activity through signaling pathways not shared with other cytokines; specifically the Act-1 adapter (actin inducing gene type 1) coupled with IL-17R makes the ubiquitination of TRAF-6 (tumoral necrosis factor [TNF] receptor associated factor type 6) and this in turn ubiquitinates the TAK-1 (TGF- β associated kinase 1), which finally leads to the activation of the canonical pathway of NF-kβ.[34,35]

IL-17A and IL-17F are involved in processes of inflammation were the predominant cell is the neutrophil, specifically the cytokine 17 has been related as a cytokine that responds to infectious processes by extracellular microorganisms, chronic autoimmune inflammatory processes, hypersensitivity reactions (asthma), and antitumor response.[22] The cellular targets of IL-17 include: fibroblasts, epithelial cells (endothelium and mucosae), dendritic cells, macrophages, osteoblasts, chondrocytes and B lymphocytes. In these cellular targets IL-17 exerts its action by regulating the high expression of chemoattractant factors CXCL (chemokine C-X-C motif ligand) and CCL (chemokine C-C motif ligand), proinflammatory cytokines, matrix metalloproteinases (MMP), TNF-α and granulocyte-macrophage colony-stimulating factor GM-CSF.[36] Evidence of the foregoing comes from trials of enzymatic microarray that have demonstrated: 1) fibroblasts, the IL-17 enhances the expression of IL-6, chemokines, growth factors and MMP which altogether induce the destruction of extracellular matrix, related to processes such as multiple sclerosis and Crohn's disease. 2) The macrophage and the dendritic cell induce an increase in the production and release of IL-1β, TNF-α, IL-6 and C-reactive protein, whose ultimate biological effect is the inflammation in conditions such as infection, psoriasis and graft versus host disease. 3) The endothelial cell increases the release of IL-6 and MMP, responsible for the vascular activation and the resulting onset of phenomena of atherosclerosis, thrombosis and tissue reperfusion injury. 4) The osteoblasts and the chondrocytes stimulate the expression of RANK, which is the receptor for RANKL, through the RANK-RANKL interaction the osteoblasts are activated and induce the osteoclastogenesis responsible for the bone resorption and the damage of the cartilages in entities such as RA, periodontal disease and loss of prosthesis.[12,23]

IL-22: Member of the family of cytokines related to IL-10, produced by Th17 lymphocytes, NK-22, lymphoid tissue inducer (LTi) cells, and epithelial cells. Its action is exerted through its IL-22R receptor (heterodimeric complex IL-22RA1/IL-10R2), specifically the interaction IL-22/IL-22R activates several tyrosine kinase-dependent signal transduction pathways (Jak1, TyK2, MAP kinases, ERk1/2) that end in the activation of the transcription factor STAT3 and then the expression of related genes. Physiologically IL-22 promotes the defense and reparative epithelial response of the mucosae through the induction of cytokines, chemokines, acute-phase proteins, β-defensins and lipocalins. Currently, it is not clear whether it exists, and in case of existing which would be the potential pathogenic role of IL-22 in autoimmune diseases such as RA or inflammatory bowel disease.[21,37]

IL-21: Produced by Th17, NK, NKT and Th17 lymphocytes, IL-21 is a member of the family of the IL-2-related cytokines, it exerts its action through its receptor which shares structural homology with the receptor for IL-2 at the α chain level. IL-21 is a pleiotropic cytokine which induces a variety of functions in the CD4+, CD8+ T cells and B lymphocytes. By functioning in an autocrine manner, IL-21 is responsible for inducing *de novo* and amplifying the differentiation of the Th17 lymphocytes in case of absence of the IL-6 signal; it is also responsible for strengthening their phenotype by stimulating the expression of the IL-23R that, as mentioned, is basic for the survival of this lineage of T lymphocytes. IL-21 exerts a dual action on the maturation of B lymphocytes. It first activates the JAK-STAT pathway required for the formation of follicular T helper cells (follicular T helper: subset of T cells retained in the lymph node, essential for the maturation of the B lymphocyte, which arise from "naive" CD4+ cells that enter into the lymph node), and second, the IL-21 stimulates the formation of germinal centers in lymphoid organs through the control of the expression of Bcl-6, which regulates the survival and activation of B lymphocytes.[22,30,37]

Pathophysiological Role of Th17 Lymphocytes and Related Cytokines in SLE

Multiple studies in human and murine models have contributed to the understanding of the pathophysiological pathways involved in the development of SLE. One of those, of relative recent description, is the pathway of the Th17 lymphocyte and IL-17A/IL-17F. The evidence of the pathophysiological role of IL-17 comes from studies that have shown that the production of IL-17 is abnormally elevated in patients with SLE, as demonstrated by the increased serum levels of this cytokine when comparing patients with SLE vs. healthy controls, matched by age and gender.[38-40] In addition, the frequency of IL-17 producing T cells is increased in the peripheral blood of SLE patients.[41] Regarding the laboratory mouse models is worth mentioning some relevant; for example, the BXD2 is a hybrid strain of mice that develop a lupus-like syndrome in an age-dependent manner; this model demonstrated the presence of circulating anti-DNA antibodies, anti-histone antibodies, splenomegaly, nephritis, erosive arthritis and increased frequency of circulating Th17 lymphocytes in peripheral blood and deposited in target organs, which resulted in increased tissue and circulating levels of IL-17.[42] MRL/*lpr* is a classical model of spontaneous lupus, characterized by the production of autoantibodies, development of glomerulonephritis and accumulation of CD4/CD8-/- T cells and Th17 lymphocytes, these cells dependent on the IL-23 survival signal were able to produce a sufficient circulating amount of IL-17, which was demonstrated by immunofluorescence and immunohistochemistry, they infiltrate the kidney and induce glomerulonephritis; as the expression of IL-17 increases, the complement-mediated renal damage increases proportionally.[43]

The capability to induce local inflammation (target organs: kidney, skin) and direct the response of the B lymphocytes is what has allowed to postulate the pathophysiological role of IL-17 in SLE. Punctually, the 17A and 17F related cytokines are cytokines with potent capability to induce tissue inflammation through the secretion of chemokines such as the monocyte chemoattractant protein-1, the growth-related oncogene protein-alpha, IL-8,IL-9, CCL2, CCL3, IL-1β, GM-CSF, which altogether are responsible for the proliferation, maturation and recruitment of neutrophils and monocytes.[37] IL-17A also facilitates the activation and infiltration of more T cells in the inflamed tissues by the upregulation of the expression of the intercellular adhesion molecule-1 (ICAM-1).[44] In conjunction to the foregoing, IL-17 induces tissue damage by positively

regulating the expression of matrix metalloproteinases (MMP-1, MMP-3, MMP-9, MMP-13) and stimulating the dendritic cell and the macrophage to increase the production of IL-1, IL-6 and TNF-α. IL-17, besides acting as a mediator of inflammation, also acts as a direct regulator of the function of B lymphocytes, specifically this cytokine promotes the survival of the B lymphocyte through the NF-κβ and the B-lymphocytes activating factor (BAFF), it also alters the deletion of clones of autoreactive B lymphocytes, breaks-up the programmed cell death program of the B lymphocyte and favors the differentiation of the B lymphocyte into plasma cell. All the above results in an increased production of autoantibodies, formation of germinal centers and retention of B lymphocytes in the target organs.[22,37]

Role of the Th17 Cytokine as a Biomarker of Disease Activity in Patients With SLE

As previously mentioned, there is clear evidence of the pathophysiologic role played by IL-17 and the cells that produce it in SLE; however, based on the literature review, an agreement regarding the role of IL-17 as a biomarker of disease activity in SLE was not found, the above due to the divergence in the results found in studies that have addressed this query. Below we present a summary of the main articles in favor of and against the usefulness of this cytokine.

Chen et al., from the Division of Allergy, immunology and Rheumatology of the Faculty of Medicine of the National Yang Ming University of Taiwan, conducted in 2012 an observational study in 24 patients with lupus nephritis (17 class IV and 7 class V) and 12 controls with minimal change nephropathy; the purposes of this study were 1) to quantify the frequency of Th-17 and related cytokines in peripheral blood in each of the study groups and 2) to measure the glomerular concentration of IL related with Th17. The measurement of the frequency (concentration) of Th-17 cells in peripheral blood was done using flow cytometry and the concentration of Th17 related cytokines was measured by the ELISA technique; also by immunohistochemistry was assessed the glomerular expression of Th17 related cytokines. The authors found: 1) the frequency of Th17 lymphocytes in peripheral blood was significantly higher in patients with SLE 0.68% vs. controls 0.12%; 2) a statistically significant difference between the concentration of IL-17 in the patients with SLE compared with the controls (7.26 pg/ml vs. 0.82 pg/ml $p < 0.001$); 3) the frequency of Th17 lymphocytes in peripheral blood was positively correlated with the SLEDAI, the renal SLEDAI and the histological activity index; 4) significantly higher glomerular levels of IL-17 were found in lupus nephritis IV vs. healthy controls or minimal change nephropathy; 5) the levels of IL-17 were positive correlated with the renal SLEDAI and the histological activity index.[45]

In the year 2000, Wong et al., in the Division of Pathology of the Prince of Wales University Hospital of Hong Kong, conducted a study with 36 Chinese patients with SLE (according to the 1982 ACR criteria) and with 18 healthy controls (matched by age and sex); the objectives of this study were to measure comparatively the levels of IL-17, 12 and 18 between the study groups, as well as to measure and evaluate the association between the relationship of IL-17/IL-4, IL-18/IL-4, IL-12/IL-4 with the SLEDAI; for this purpose they took 20 ml of peripheral blood (peripheral blood mononuclear cells) of each of the participants, subsequently they froze the sample at –70 °C for storage and once the experimental part was executed they measured by ELISA the serum concentrations of IL-17, IL-18, IL-4, IL-6. In their results they reported that the concentration of IL-17 was significantly higher among the patients with lupus compared with the controls (76.5 ± 45.7 vs. 37.6 ± 35.3 (pg/ml) P 0.002), however, they did not find a good correlation of the relationship between IL-17/IL-4 and the disease activity measured by SLEDAI (*r* 0.047, *P* value 0.777).[38]

In 2008, another work was conducted by Wong et al., in which they took 80 Chinese patients (78 women and 2 men) with SLE according to the 1982 ACR criteria; they distributed them into SLE patients with renal involvement (RSLE 40) and SLE without renal involvement (SLE 40) and compared them with 46 healthy controls; the study sought to: 1) measure comparatively the number of circulating Th-17 cells; 2) measure the production of IL-17 by peripheral blood mononuclear cells (PBMC) stimulated with anti-CD3 and anti-CD28 as well as to measure the production of IL-17 by Th-17 cells; 3) examine the clinical significance of the measurement of the concentration of IL-17. They measured and defined the disease activity by SLEDAI (> 6: activity). For the execution of the technical part of the study they took 20 mL of peripheral blood collected in tubes containing EDTA, then, maximum one hour after, the PBMC were separated from the whole blood and cultured with anti-CD3, anti-CD28 and IL-23/18 for a period of 24 hours at 37 °C, Finally, from this cell culture was obtained a cell-free supernatant that was stored for subsequent measurement of cytokines by the ELISA technique. They found that: 1) the levels of IL-17 were higher in patients with RSLE (22.44 pg/mL ± 21.37-25.14) and SLE (25.14 pg/mL ± 22.79-30.36) vs. healthy controls IL-17 (6.55 pg/mL ± 5.69-7.89) and 2) the levels of IL-17 were positively correlated with the disease activity measured by SLEDAI (Pearson's *r* 0.359, *P* 0.022).[46]

In 2013, the group of Dr. Enass A. Elewa, from the Zagazig University, in Egypt, published an observational analytical study whose objectives were: 1) to establish the correlation between the level of proinflammatory cytokines (IL-4, IL-17) and the disease activity in SLE measured by SLEDAI, and 2) to establish whether these cytokines could be used as biomarkers of renal activity. To do this, they took 40 patients with SLE and compared them with 30 matched controls (apparently healthy individuals), they worked with the serum of each patient, obtained from peripheral blood and they measured the concentration of cytokines by ELISA. In this study it was observed that: 1) there were statistically significant differences between the levels of IL-17 in patients with SLE vs. controls (37 ng/L (0.5-102) vs. 6.75 ng/L (0.5-14) *P* 0.00) and 2) there was a positive correlation between the levels of IL-17 and the SLEDAI score, from which it was possible to establish the following operational performance: IL-17 (> 11.5 [cut-off point]) S: 77.5% E: 83.3% PPV: 86.1 NPV: 73.5% AUC 0.811 CI 95%: 0.701-0.922 < 0.05.[47]

Xue-Fei Zhao et al., belonging to the Departments of Biostatistics, Public Health and Rheumatology of the University Hospital of Anhui, in the Republic of China, con-

ducted an observational study that sought to measure the serum levels of IL-17 and their association with the clinical manifestations and the disease activity; for this purpose they chose 57 patients with diagnosis of SLE (according to the1982 ACR criteria) who served as cases (55 women and 2 men) and 30 healthy controls (29 women and 1 man), they stratified this population according to the renal involvement; they took 5 ml of peripheral blood of each patient, which was centrifuged and subsequently they stored the serum at –80 °C until they performed the test, finally they measured the levels of IL-17 by ELISA. The authors found that: 1) the levels of IL-17 were significantly elevated in patients with SLE compared with controls (SLE without lupus nephritis 24.70 pg/mL ± 8.43 vs. control 16.98 pg/mL ± 5.98 *P* 0.002, and SLE with lupus nephritis 22.41 pg/mL ± 9.64 vs. control 16.98 pg/mL ± 5.98 *P* 0.002); 2) it was not evidenced an association between the levels of IL-17 and the paraclinical and clinical parameters that make up the SLEDAI (Tables 2 and 3 of the original article); 3) differences in the levels of IL-17 between the patients with SLE with nephritis vs. SLE without nephritis were not found and 4) there were no differences in the levels of IL-17 between the patients with lower activity vs. higher activity.[48]

In the Public University of Monash, Australia, in 2013, Drs. Fabien B Vincent and Melissa Northcott conducted a prospective observational study in which they sought to examine whether there was an association between the serum concentration of IL-17 and the expression of the disease in terms of activity measured by the SLEDAI-2k/2000 (it corresponds to a modification of the original SLEDAI, used only in clinical trials on the prognosis of SLE). For this purpose, they included in their study patients older than 18 years who met the 1982 ACR criteria for SLE; the patients were recruited between May 2007 and June 2009. 98 patients with SLE (39 Asian and 57 Caucasian) were included initially; of the 98 initial patients, 75 were followed-up longitudinally (on average 3 visits [2-10]) each on average every 12 weeks, so that counting from the beginning of the study it was possible to collect 343 sera. It was found that the serum levels of IL-17 did not correlate with the STD (SLEDAI-2k, anti- DNAds, CRP, ESR) measures of disease activity and that when the sera were categorically separated according to SLEDAI-2k (< 4: inactive; > 4 but < 8: mild activity; > 8, 12, 16 or 18: high activity) no differences were found between the levels of IL-17, and 3. During the follow-up period, no association was found between the variation (Δ = Delta) of the levels of IL-17 and the Δ of the disease activity.[49]

Drs. Cheng, Guo, et al., from the Departments of Pneumology, Rheumatology and Immunology of the Changzheng Hospital in Shanghai, China, carried out an observational clinical that sought to analyze the profile of plasma cytokines related to Th-17 cells. They recruited 45 patients (22 women and 23 men) and 32 healthy controls, they measured the levels of cytokines by ELISA technique and defined the disease activity as a SLEDAI > 6. The findings were as follows: 1) the levels of IL-17 were higher in patients with active SLE vs. controls (79.0 pg/ml (25.4-454.6) vs. 36.4 pg/ml (15.7-338.2); $P < 0.001$) as well, the levels of IL-17 were also higher in patients with non-active SLE vs. controls (77.8 pg/ml (27.5-487.6) vs. 36.4 pg/ml (15.7-338.2; $P < 0.01$); however, in the direct comparison between active and non-active, there were no statistically significant differences. 2) There is a slight positive correlation and also without statistical significance between IL-17 and SLEDAI. In that way, the authors point out that the increased levels of IL-17, IL-23 and decreased levels of IL-22 suggest a pathophysiological role for these IL in SLE, but that the role that IL-17 y 23 might play as biomarkers of disease activity still remains unclear.[50]

Conflict of Interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Gualtierotti R, Biggioggero M, Penatti AE, Meroni PL. Updating on the pathogenesis of systemic lupus erythematosus. Autoimmun Rev. 2010;10(1):3-7.
2. Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365(22):2110-21.
3. Gatto M, Zen M, Ghirardello A, Bettio S, Bassi N, Iaccarino L, et al. Emerging and critical issues in the pathogenesis of lupus. Autoimm Rev. 2013;12(4):523-36.
4. D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematosus. Lancet. 2007;369(9561):587-96.
5. Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med. 2008;358(9):929-39.
6. Bluestone JA, Mackay CR, O'Shea JJ, Stockinger B. The functional plasticity of T cell subsets. Nat Rev Immunol. 2009;9(11):811-6.
7. Liu Z, Davidson A. Taming lupus-a new understanding of pathogenesis is leading to clinical advances. Nat Med. 2012;18(6):871-82.
8. Mosmann TR, Coffman RL. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional propertiesJT Annu Rev Immunol. 1989;7:145-73.
9. Hsieh CS, Macatonia SE, Tripp CS, Wolf SF, O'Garra A, Murphy KM. Development of TH1 CD4+ T cells through IL-12 produced by Listeria-induced macrophages. Science (New York, NY). 1993;260(5107):547-9.
10. Ansel KM, Djuretic I, Tanasa B, Rao A. Regulation of Th2 differentiation and Il4 locus accessibility. Annu Rev Immunol. 2006;24:607-56.
11. Bettelli E, Korn T, Kuchroo VK. Th17: the third member of the effector T cell trilogy. Curr Opin Immunol. 2007;19(6):652-7.
12. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. Annu Rev Immunol. 2009;27:485-517.
13. Cheng X, Yu X, Ding YJ, Fu QQ, Xie JJ, Tang TT, et al. The Th17/Treg imbalance in patients with acute coronary syndrome. Clin Immunol. 2008;127(1):89-97.
14. Wang X, Ma C, Wu J, Zhu J. Roles of T helper 17 cells and interleukin-17 in neuroautoimmune diseases with emphasis on multiple sclerosis and Guillain-Barre syndrome as well as their animal models. J Neurosci Res. 2013;91(7):871-81.
15. Azizi G, Jadidi-Niaragh F, Mirshafiey A. Th17 Cells in Immunopathogenesis and treatment of rheumatoid arthritis. Int J Rheum Dis. 2013;16(3):243-53.
16. Siakavellas SI, Bamias G. Role of the IL-23/IL-17 axis in Crohn's disease. Discov Med. 2012;14(77):253-62.
17. Smith JA, Colbert RA. Review The interleukin-23/interleukin-17 axis in spondyloarthritis pathogenesis: Th17 and beyond. Arthritis Rheumatol. 2014;66(2):231-41.

18. Kirkham BW, Kavanaugh A, Reich K. Interleukin-17A: a unique pathway in immune-mediated diseases: psoriasis, psoriatic arthritis and rheumatoid arthritis. Immunol. 2014;141(2):133-42.
19. Suzuki E, Mellins ED, Gershwin ME, Nestle FO, Adamopoulos IE. The IL-23/IL-17 axis in psoriatic arthritis. Autoimmun Rev. 2014;13(4-5):496-502.
20. Garrett-Sinha LA, John S, Gaffen SL. IL-17 and the Th17 lineage in systemic lupus erythematosus. Curr Opin Rheumatol. 2008;20(5):519-25.
21. Abul K, Abbas AHL, Shiv Pillai. In: Saunders E, editor. Cellular and molecular immunology. 7.ª ed. California: San Francisco; 2012. p. 173-201.
22. Jiang S. TH17 Cells in health and disease. New York: Springer Science+Business Media; 2011. p. 3-26.
23. Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. N Eng J Med. 2009;361(9):888-98.
24. Huang G, Wang Y, Chi H. Regulation of TH17 cell differentiation by innate immune signals. Cell Mol Immunol. 2012;9(4):287-95.
25. Nalbandian A, Crispin JC, Tsokos GC. Interleukin-17 and systemic lupus erythematosus: current concepts. Clin Exp Rheumatol. 2009;157(2):209-15.
26. Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, Elson CO, et al. Transforming growth factor-beta induces development of the T(H)17 lineage. Nature. 2006;441(7090):231-4.
27. McGeachy MJ, Chen Y, Tato CM, Laurence A, Joyce-Shaikh B, Blumenschein WM, et al. The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells in vivo. Nat Immunol. 2009;10(3):314-24.
28. Oppmann B, Lesley R, Blom B, Timans JC, Xu Y, Hunte B, et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity. 2000;13(5):715-25.
29. Nurieva R, Yang XO, Martínez G, Zhang Y, Panopoulos AD, Ma L, et al. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. Nature. 2007;448(7152):480-3.
30. Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, et al. IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. Nature. 2008;454(7202):350-2.
31. Rouvier E, Luciani MF, Mattei MG, Denizot F, Golstein P. CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a herpesvirus saimiri gene. J Immunol. 1993;150(12): 5445-56.
32. Fossiez F, Djossou O, Chomarat P, Flores-Romo L, Ait-Yahia S, Maat C, et al. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. J Exp Med. 1996;183(6):2593-603.
33. Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. Annu Rev Immunol. 2007;25:821-52.
34. Martin JC, Baeten DL, Josien R. Emerging role of IL-17 and Th17 cells in systemic lupus erythematosus. Clin Immunol. 2014;154(1):1-12.
35. Gaffen SL. Structure and signalling in the IL-17 receptor family. Nat Rev Immunol. 2009;9(8):556-67.
36. Zhu S, Qian Y. IL-17/IL-17 receptor system in autoimmune disease: mechanisms and therapeutic potential. Clin Sci (London, England: 1979). 2012;122(11):487-511.
37. Perry D, Peck AB, Carcamo WC, Morel L, Nguyen CQ. The current concept of T (h) 17 cells and their expanding role in systemic lupus erythematosus. Arthritis. 2011;2011:810649.
38. Wong CK, Ho CY, Li EK, Lam CW. Elevation of proinflammatory cytokine (IL-18, IL-17, IL-12) and Th2 cytokine (IL-4) concentrations in patients with systemic lupus erythematosus. Lupus. 2000;9(8):589-93.
39. Tanasescu C, Balanescu E, Balanescu P, Olteanu R, Badea C, Grancea C, et al. IL-17 in cutaneous lupus erythematosus. Eur J Intern Med. 2010;21(3):202-7.
40. Chen XQ, Yu YC, Deng HH, Sun JZ, Dai Z, Wu YW, et al. Plasma IL-17A is increased in new-onset SLE patients and associated with disease activity. J Clin Immunol. 2010;30(2):221-5.
41. Crispin JC, Oukka M, Bayliss G, Cohen RA, Van Beek CA, Stillman IE, et al. Expanded double negative T cells in patients with systemic lupus erythematosus produce IL-17 and infiltrate the kidneys. J Immunol. 2008;181(12):8761-6.
42. Hsu HC, Yang P, Wang J, Wu Q, Myers R, Chen J, et al. Interleukin 17-producing T helper cells and interleukin 17 orchestrate autoreactive germinal center development in autoimmune BXD2 mice. Nat Immunol. 2008;9(2):166-75.
43. Zhang Z, Kyttaris VC, Tsokos GC. The role of IL-23/IL-17 axis in lupus nephritis. J Immunol. 2009;183(5):3160-9.
44. Apostolidis SA, Crispin JC, Tsokos G.C.I.L-17-producing. T cells in lupus nephritis. Lupus. 2011;20(2):120-4.
45. Chen DY, Chen YM, Wen MC, Hsieh TY, Hung WT, Lan JL. The potential role of Th17 cells and Th17-related cytokines in the pathogenesis of lupus nephritis. Lupus. 2012;21(13):1385-96.
46. Wong CK, Lit LC, Tam LS, Li EK, Wong PT, Lam CW. Hyperproduction of IL-23 and IL-17 in patients with systemic lupus erythematosus: implications for Th17-mediated inflammation in auto-immunity. Clin Immunol. 2008;127(3):385-93.
47. Elewa EA, Zakaria O, Mohamed EI, Boghdadi G. The role of interleukins 4, 17 and interferon gamma as biomarkers in patients with Systemic Lupus Erythematosus and their correlation with disease activity. Egypt Rheumatol. 2014;36(1):21-7.
48. Zhao XF, Pan HF, Yuan H, Zhang WH, Li XP, Wang GH, et al. Increased serum interleukin 17 in patients with systemic lupus erythematosus. Mol Biol Rep. 2010;37(1):81-5.
49. Vincent FB, Northcott M, Hoi A, Mackay F, Morand EF. Clinical associations of serum interleukin-17 in systemic lupus erythematosus. Arthritis Res Ther. 2013;15(4):R97.
50. Cheng F, Guo Z, Xu H, Yan D, Li Q. Decreased plasma IL22 levels, but not increased IL17 and IL23 levels, correlate with disease activity in patients with systemic lupus erythematosus. Ann Rheum Dis. 2009;68(4):604-6