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BAFF-R and TACI expression on CD3+ T cells: Interplay among BAFF, APRIL and T helper cytokines profile in systemic lupus erythematosus

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is the prototype of systemic autoimmune disease, characterized by loss of immune tolerance against self-antigens where autoantibody production is the hallmark of disease. B-cell-activating factor (BAFF) and A proliferation-inducing ligand (APRIL) are cytokines that promote autoreactive cell survival, immunoglobulin-class switching and autoantibody responses in human and mouse SLE models. BAFF and APRIL exert their functions through interactions with their receptors BAFF-R and TACI that are differentially expressed in B lymphocyte subsets, monocytes, dendritic cells and T lymphocytes. BAFF stimulation favors T lymphocyte activation and cytokine production through BAFF-R, which could contribute to the Th1, Th17 and/or Th2 response dysregulation observed in SLE patients.

Objective: To evaluate the expression of the cytokines BAFF and APRIL and their association with the receptors BAFF-R and TACI on CD3+ T cells and to evaluate Th1/Th2/Th17 cytokine profile in patients with SLE.

Methods: Fifteen healthy controls (HC) and 36 SLE patients were included, and their demographic and clinical data were assessed. The disease activity index (Mex-SLEDAI) and damage index (SLICC) were applied to the SLE patients. BAFF-R and TACI expression on CD3+ T cells were evaluated by flow cytometry. Serum BAFF and APRIL concentrations were measured by enzyme-linked immunosorbent assays (ELISA). Cytokine levels of Th1 (IL-12, IL-2, IFN-γ, TNF-α), Th2 (IL-4, IL-6, IL-10, IL-13) and Th17 (IL-1β e IL-17) were quantified with a multiplex assay (MAGPIX). Statistical analysis was performed using PASW Statistics v.20 and GraphPad Prism v.6 software.

Results: No differences in BAFF-R or TACI expression on the CD3+ T cells of SLE and HC were observed. BAFF-R expression correlates inversely with disease activity ($r = -0.538$, $p < 0.01$), while TACI correlates with disease activity ($r = 0.530$, $p < 0.05$). Serum BAFF and APRIL levels were high in SLE patients and correlated with the disease activity index Mex-SLEDAI ($r = 0.621$, $p < 0.01$ and $r = 0.416$, $p < 0.05$). SLE patients were found to have significantly higher levels of IL-12, IFN-γ, TNF-α, IL-6, IL-10, IL-13, IL-1β and IL-17 compared to HC ($p < 0.05$). Cytokines IL-17 ($r = 0.526$) and TNF-α ($r = 0.410$) correlate with disease activity ($p < 0.05$), while APRIL ($r = 0.477$), IL-10 ($r = 0.426$) and IFN-γ ($r = 0.440$) levels were associated with organ damage ($p < 0.01$). Serum BAFF expression levels correlate with IL-4 ($r = 0.424$; $p < 0.05$), IL-6 ($r = 0.420$; $p < 0.05$) and IL-10 ($r = 0.459$; $p < 0.01$), whereas APRIL levels correlate with IL-2 ($r = 0.666$; $p < 0.01$), IL-12 ($r = 0.611$; $p < 0.01$) and TNF-α ($r = 0.471$; $p < 0.05$) cytokines. A subgroup of SLE patients with high serum BAFF levels (> 2 ng/mL) also showed increased APRIL, IL-2, IL-6 and IL-10 levels ($p < 0.05$). Finally, BAFF, IL-4 and TNF-α serum levels were associated with high titers of antinuclear antibodies.

Conclusions: The study demonstrates an imbalance in the Th1/Th2 cytokine profile, with increased proinflammatory cytokines, as well as BAFF and APRIL serum levels. Associations of BAFF with Th2 profile cytokines and disease activity, as well as APRIL with Th1 profile cytokines and organ damage, suggest that BAFF and APRIL generated in the autoimmunity context could through still unknown mechanisms, modulate the microenvironment, and perpetuate the inflammatory response, autoantibody production and organ damage observed in SLE patients.

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1. Introduction

Systemic lupus erythematosus (SLE) is the prototype of systemic autoimmune disease, characterized by loss of immune tolerance against self-antigens where autoantibody production is the hallmark of disease [1]. Unrestricted hyperactivation of the immune system might lead to the overproduction of autoantibodies, immune complex deposition and inflammatory cytokine release [2]. Cytokines are important components of immune response and can be generated by both innate and adaptive immune cells exerting different effects depending on the local microenvironment [3]. They can also interact with each other, forming a complex network to maintain the delicate immune homeostasis [2]. An imbalance between pro- and anti-inflammatory cytokines is a well-known characteristic of SLE [4]. Several studies have shown that B-cell and T-cell hyperactivity and autoantibody production were associated with elevated levels of proinflammatory cytokines [5], contributing to the broad spectrum of clinical manifestations observed in SLE patients including the skin, joints, the central nervous system and the kidneys [6].

The B cell-stimulating molecules A PRoliferation-Inducing Ligand (APRIL) and B-cell-activating factor (BAFF) are cytokines that have received major attention in SLE pathogenesis because they promote autoreactive lymphocytes survival, immunoglobulin-class switching and autoantibody responses in human and mice SLE models [7,8]. Increased serum levels of BAFF and APRIL have been associated with disease activity [9–18] and autoantibody titers [12,15,19,20] in SLE patients. These cytokines exerts their functions through interactions with their receptors, the BAFF receptor (BAFF-R), the transmembrane activator and cyclophilin ligand interactor (TACI) and B- cell maturation antigen (BCMA), who are differentially expressed in B cell subsets [21–24], monocytes [25], dendritic cells [26] and T cells [27,28]. The contribution of BAFF and APRIL has been well stablished in the context of B cell function, giving them a key role as regulators of the composition and size of B cell compartment, and in the establishment and maintenance of immune responses, including antibody production [7,29]. Nevertheless, controversy remains regarding the contribution of BAFF-R and TACI in T cell function. In a murine SLE model, BAFF neutralization reduced the activation of T cells at an earlier stage of the disease, favoring the remission of SLE activity [30], while other researchers found that BAFF stimulation favors T cell activation and cytokine production through BAFF-R [31–33]. In this context, the aims of this work were to associate the costimulatory effect of BAFF and APRIL through BAFF-R and TACI on CD3+ T cells and the cytokine serum profiles in SLE patients.

2. Materials and methods

2.1. Study population

Thirty-six SLE patients fulfilling at least four of the American College of Rheumatology revised criteria for SLE (Hochberg, 1997) without any concurrent infections were recruited from the Rheumatology Department of the West General Hospital, Mexico, and fifteen healthy controls (HC), matched by age and gender, were recruited from personnel at the Hospital. Disease activity was assessed by the Mexican version of the Systemic Lupus Erythematosus Disease Activity Index (Mex-SLEDAI) [34] and the Systemic Lupus International Collaborating Clinics index (SLICC) [35] were applied to the SLE patients at the enrollment of the study. Appropriate ethical and biosecurity conduct was ensured by the Declaration of Helsinki guidelines and was also evaluated and approved by the institutional Ethics Committee. Before enrollment, the participants gave their signature in a consent document after they were informed about all implications of the study.

2.2. Sampling

Venous blood samples were drawn into Ethylene Diamine Tetra acetic acid (EDTA) and serum sterile tubes from patients and healthy subjects. Whole blood was allowed to clot and centrifuged at 1500 rpm for 10 min. Serum samples were separated and divided into aliquots and then stored at -80 °C for subsequent cytokine analysis.

2.3. Laboratory and clinical assessment

A clinical assessment was performed in all individuals at the time of enrollment, including determinations of complete blood count (CELL-DYN 3500R; Abbott Diagnostics, Abbott Park; IL, USA) and erythrocyte sedimentation rate (ESR) (Wintrobe method). All participants completed a questionnaire to gather personal and family medical history. The autoantibody profile was as follows: antinuclear autoantibodies (ANAs), double strain DNA (dsDNA), anti-Ro, anti-La, anti-Sm and anti-RNP were collected from patients' records.

2.4. Flow cytometry

For the identification of BAFF-R and TACI on $CD3^+$ T cells, peripheral blood mononuclear cells (PBMCs) were obtained by centrifugation over a Ficoll-paque gradient (Sigma Aldrich, Saint Louis, MO, USA). The cells were then washed twice and the pellet was stained in the dark for 30 min with fluorochrome-conjugated antibodies: anti-human allophycocyanin/Cy7 (APC/Cy7)- conjugated anti-CD3 at 5 μg/mL, peridinin chlorophyll protein-conjugated (PerCP)-anti-CD19 at 5 μg/mL, phycoerythrin (PE)- conjugated anti-268 (BAFF-R) at 5 μg/mL, PE-conjugated anti-267 (TACI) at 5 μg/mL and their corresponding isotypes (BioLegend Inc, San Diego, CA, USA). Briefly, at the end of the labeling, the cells were pelleted and washed twice with 1% Phosphate Buffered Saline (PBS) before acquisition on a FACS Aria I cytometer (BD Biosciences, San Jose, CA, USA). For each sample, at least 50,000 lymphocytes were acquired. The appropriate isotype and Fluorescence Minus One (FMO) controls were used to adjust for background fluorescence and gates, and the results are reported as the percentage (%) of expression and the mean fluorescence intensity (MFI). Data were processed with FACSDiva software (BD Biosciences).

2.5. Immunological assays

2.5.1. BAFF and APRIL quantification

Soluble BAFF and APRIL levels were quantified from the sera of SLE patients and HS with quantitative sandwich enzyme immunoassay technique (R&D Systems, Minneapolis, MN, USA) performed following recommendations from the manufacturer. After adding stop solution, the intensity was measured by an automated microplate reader at 450 nm (BioTek Instruments, Inc., Winooski, VT, USA).

2.5.2. Th1/Th2/Th17 cytokine quantification

The serum levels of the cytokines Th1 (IL-12, IL-2, IFN-γ, TNF-α), Th2 (IL-4, IL-6, IL-10, IL-13) and Th17 (IL-1β e IL-17) were determined by the Invitrogeńs Novex human Th1/Th2/Th17 Magnetic 10-Plex Panel assay (Millipore, Billerica, MA, USA) which utilizes Luminex xMAP® technology. Briefly, SLE patients and HC sera were incubated with magnetic microspheres who are internally dyed with red and infrared fluorophores of differing intensities and a distinct coat of capture antibodies specific for each one of the analytes being tested. Each bead

is given a unique number, or bead region, allowing differentiation of one bead from another. A biotinylated detection antibody was then introduced followed by incubation with streptavidin-phycoerythrin, which acted as the reporter molecule on the surface of each microsphere. At the completion of the sandwich immunoassay, beads were read on the Bio-RAD MAGPIX® instrument. Briefly, two light-emitting diodes (LEDs) were used to excite the internal dyes marking each microsphere set and the dye in the reporter molecule followed by a CCD camera for bead and analyte detection, and high-speed digital signal processors were used to quantify the reporter signals from each bead set.

2.6. Statistical analyses

Data are expressed as the mean ± SE or median (interquartile range [IQR]). The Mann–Whitney *U* test was used to compare MFI and receptor percentage on $CD3^+$ T cells and cytokine levels in SLE group with those in HC. Kruskal–Wallis with Dunn´s test as post hoc were applied for multiple comparisons. Spearman correlation was used to compare changes in the levels of biomarkers, cytokines and disease activity in SLE patients. The Statistical Package for Social Sciences (SPSS) version 20 (LEAD Technology Inc., Charlotte, NC, USA) and GraphPad Prism v.6 software (GraphPad Software Inc.; San Diego, CA, USA) were used to analyze the data. All p values < 0.05 were considered significant.

3. Results

3.1. Demographic and clinical characteristics

All subjects included in the study were females. The average age was 35 years old (range 22–50 years) and 32 years old (range of 18–64) for HC and SLE subjects, respectively. The SLE patients had a mean of 6.7 years of disease duration (range 0–21 years) and presented an activity disease score of 4.6 (range of 0–18) for Mex-SLEDAI and 0.8 (range of 0–4) score for SLICC damage index. The main clinical manifestations were hematologic, renal activity, and mucocutaneous. The treatment of SLE patients included immunosuppressive drugs (azathioprine, methotrexate, cyclophosphamide, and mycophenolate), hydroxychloroquine, and prednisone (Table 1).

3.2. BAFF-R and TACI expression on CD3+ T cells

The percentage of T cells (CD3 + CD19) was similar in the SLE group (71.92 ± 10.13%) and in the HCs 67.48 ± 7.18%). No differences were observed between SLE and HC in the median expression rate and median MFI of BAFF-R (7.75% (1.18–14.88 IQR) and 2,428 (1926–3,057 IQR) vs 21.05% (10.08–23.88 IQR; $p = 0.051$) and 2,015 (1932–2,361 IQR; $p = 0.113$), respectively) (Fig. 1c). For TACI receptor in SLE, the median expression rate was 2.8% (0.725–10.15 IQR) and MFI 2,496 (1,887–3,012 IQR) and there was no difference compared to HC (1.3% (0.85–9.9 IQR); $p = 0.058$ and MFI 1,892 (1,529–2,842 IQR); $p = 0.060$) (Fig. 1d).

SLE patients were compared according to disease activity; the inactive SLE patients (median of 3,193 MFI) showed increased MFI BAFF-R expression compared with the active SLE patients (median of 2,258 MFI; $p = 0.024$). In terms of the TACI receptor, the expression was elevated in active SLE patients compared to inactive SLE (2,978 MFI (1,983–3,055 IQR) vs 1,938 MFI (1,798–2,376 IQR; $p = 0.007$) (Fig. 1c and d).

3.3. Cytokine profile

Regarding the B cell proliferation cytokines, for BAFF (Fig. 2a) and APRIL (Fig. 2b), both were significantly elevated in SLE patients compared to HC, (3.03 ± 3.91 vs 0.95 ± 0.21 ng/mL; $p < 0.001$) and (35.27 ± 27.75 vs 12.72 ± 20.02 ng/mL; $p < 0.05$), respectively.

Serum levels of Th1/Th2/Th17 cytokines were measured in all SLE patients and healthy subjects by cytokine multiplex assays. The mean serum levels of Th1 (IL-2, IL-12, IFN-γ, TNF-α) Th2 (IL-4, IL-6, IL-10, IL-13) and Th17 (IL-1β e IL-17) were significantly higher among SLE patients compared to healthy individuals.

Fig. 2 shows the distribution of serum cytokine levels among patients and control subjects. Serum levels of proinflammatory cytokines are as follows: IL-12 was significantly higher among SLE patients (262.47 ± 253.63 pg/mL) compared to HC (94.60 ± 41.84 pg/mL; $p < 0.01$). The IFN-γ levels were found to be significantly elevated (7.09 ± 2.13 vs 5.61 ± 0.63 pg/mL; $p < 0.01$); furthermore, mean serum level of TNF-α is elevated in SLE patients (41.95 ± 117.66 pg/mL) compared to HC (2.98 ± 0.50 pg/mL, $p < 0.05$). The Th2 cytokine profile was also dysregulated, with increased levels of IL-6 (23.39 ± 45.96 pg/mL) and IL-13 (4.99 ± 17.62 pg/mL) in patients compared to HC (6.20 ± 2.37 and 0.14 ± 0.20 pg/mL), respectively. This difference was statistically significant compared with healthy individuals ($p < 0.01$). In addition, the serum levels of cytokine IL-10 were elevated in SLE patients (11.10 ± 8.35 pg/mL) compared to HC (5.77 ± 0.40 pg/mL, $p < 0.001$). Finally, IL-1β high serum levels were found in SLE compared to HC (18.44 ± 43.82 vs 0.15 ± 0.60 pg/mL; $p < 0.05$), likewise mean serum level of IL-17

Table 1
Laboratory and clinical characteristics of SLE patients.

	Inactive SLE ($n = 13$) Mex-SLEDAI ≤ 2	Active SLE ($n = 23$) Mex-SLEDAI ≥ 3	p value
Age (years[a])	34.54 ± 10.58	30.30 ± 9.90	0.240[b]
Disease duration (years[a])	12.17 ± 6.67	4.03 ± 4.26	0.001[b]
Laboratory features			
WBC (κ/mm^3)	5.20 ± 2.18	7.20 ± 7.47	0.355[b]
PLT (κ/mm^3)	202.9 ± 108.0	207.9 ± 79.7	0.878[b]
ESR (mm/h)	33.20 ± 19.24	41.21 ± 17.13	0.257[b]
Autoantibodies			
ANA > 1: 640	6/13	18/23	0.049[c]
anti-dsDNA	5/13	13/23	0.297[c]
anti-Sm	3/13	7/23	0.635[c]
anti-Ro	2/13	6/23	0.458[c]
anti-La	3/13	6/23	0.841[c]
anti-RNP	3/13	3/23	0.678[c]
Clinical assessment			
Mex-SLEDAI score[a]	0.69 (0–2)	6.83 (3–18)	0.001[b]
SLICC score[a]	0.77 (0–3)	0.95 (0–4)	0.718[b]
Clinical manifestations			
Haematological (n, %)	6 (46.2%)	15 (65.2%)	0.265[c]
Mucocutaneous (n, %)	1 (7.7%)	12 (52.2%)	0.007[c]
Musculoskeletal (n, %)	1 (7.7%)	7 (30.4%)	0.114[c]
Renal disorder (n, %)	2 (15.4%)	9 (39.1%)	0.137[c]
Serous (n, %)	0 (0%)	4 (17.4%)	0.274
Neuropsychiatric (n, %)	0 (0%)	0 (0%)	0.999
Treatment			
Prednisone, n (%)	7 (53.8%)	15 (65.2%)	0.501
Azathioprine, n (%)	8 (61.5%)	11 (47.8%)	0.428
Antimalarial, n (%)	11 (84.6%)	13 (56.5%)	0.085
Cyclophosphamide, n (%)	4 (30.8%)	4 (17.4%)	0.353
Methotrexate, n (%)	1 (7.7%)	2 (8.7%)	0.916
Mycophenolate, n (%)	1 (7.7%)	3 (13%)	0.240

Data show as mean ± standard deviation. WBC: white blood cell count; PLT: platelet count; ESR: erythrocyte sedimentation rate; ANA: antinuclear antibody; Mex-SLEDAI: Mexican version of the Systemic Lupus Erythematosus Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics.

[a] Data provided in mean (min–max).

[b] Mann-Whitney *U* test.

[c] Chi-Square test or exact Fisher test.

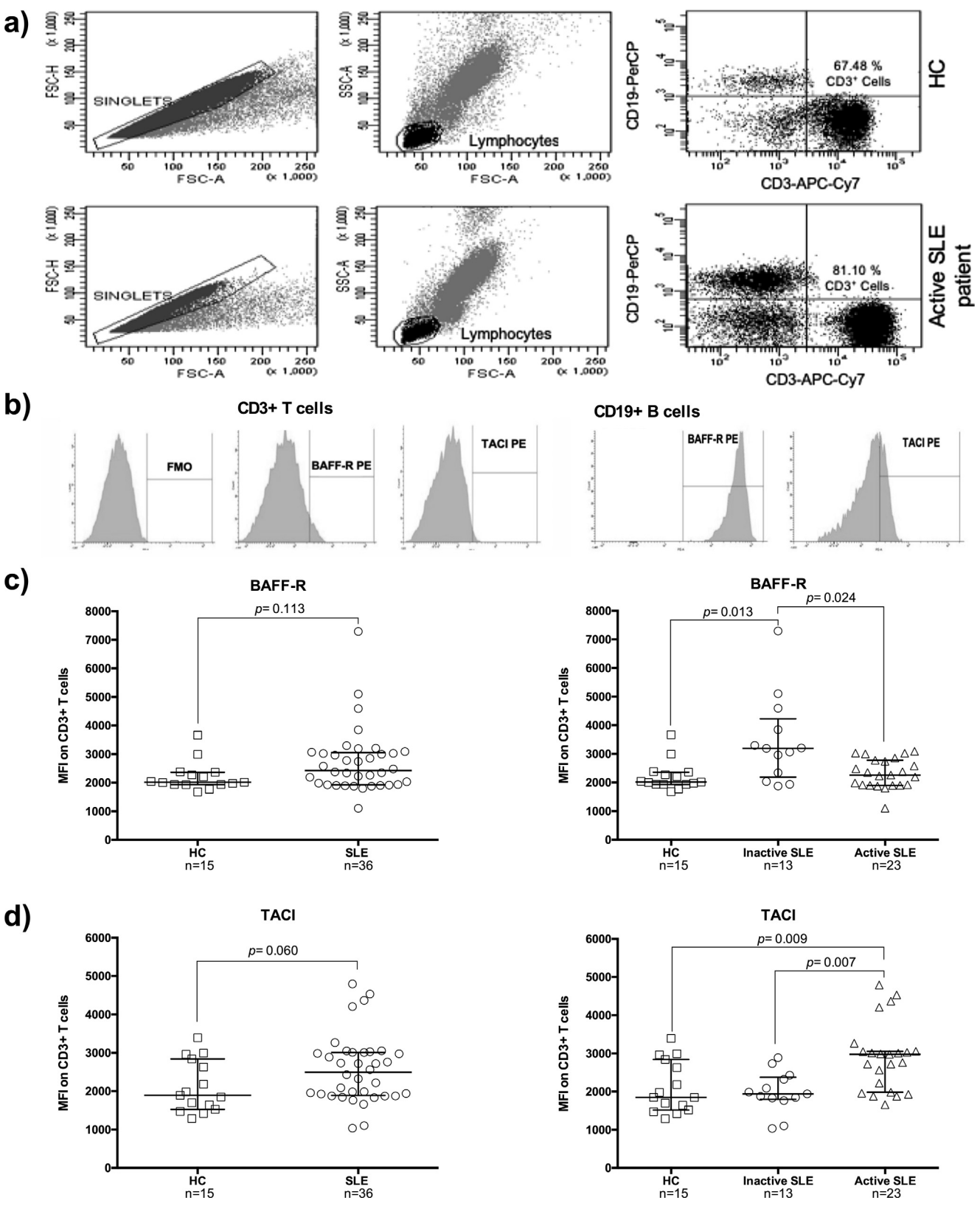

Fig. 1. Figure (a) shows representative examples of a selection of CD3+ cells from one HC and one SLE subject. Histograms showing the intensity (b) of BAFF-R and TACI on $CD3^+$ and CD19+ cells. The distribution of BAFF-R (c) and TACI (d) receptors in HC vs SLE patients with inactive and active disease. BAFF-R: B cell activating factor receptor, MFI: mean fluorescence intensity, TACI: transmembrane activator and CAML interactor. Lines depict the median and interquartile range (IQR). Statistical analysis was performed using the Mann-Whitney *U* test and Kruskal Wallis test.

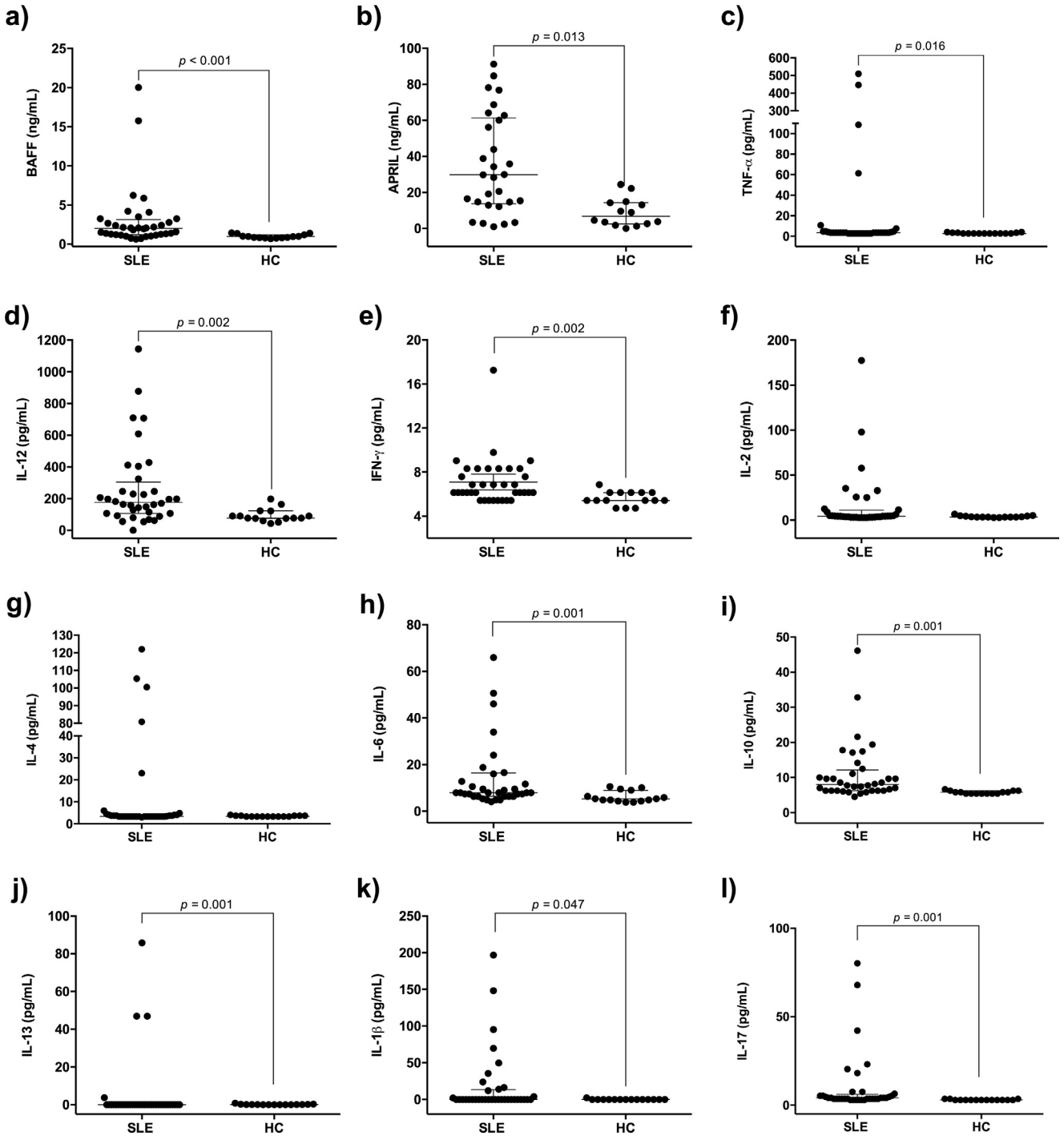

Fig. 2. Distribution of cytokine levels in systemic lupus erythematosus (SLE) patients and healthy controls (HC). Shown are serum concentrations (ng/mL) and (pg/mL) of the cytokines B cell activating factor (BAFF) (a), a proliferation-inducing ligand (APRIL) (b), tumor necrosis factor (TNF)-alpha (c), interleukin (IL)-12 (d), interferon (IFN)-gamma (e), IL-2 (f), IL-4 (g), IL-6 (h), IL-10 (i), IL-13 (j), IL-lbeta (k), IL-17 (1). Cytokines were analyzed by MAGPIX multiplex cytokine assay. Lines depict the median and interquartile range (IQR). Statistical analysis was performed using the Mann-Whitney *U* test.

was 3.5 times higher (10.46 ± 17.50) compared to HC (3.10 ± 0.24 pg/mL; $p = 0.001$).

3.3.1. Cytokine profile SLE patients with high BAFF levels

Table 2 shows BAFF-R, TACI and soluble cytokine Th1/Th2/Th17 expression levels according to the BAFF serum levels, using a cut-off of 2 ng/mL as established by Petri *et al.* as an independent predictor of relapses in SLE patients (Petri, 2013). High serum BAFF/SLE patients (≥ 2 ng/mL) had elevated Mex-SLEDAI activity index (6.61 ± 4.32) compared with low (< 2 ng/mL) BAFF/SLE patients (2.61 ± 2.66; $p = 0.003$). APRIL and cytokines IL-2, IL-6 and IL-10 were also elevated in high serum BAFF/SLE patients ($p < 0.05$). BAFF-R and TACI expression on CD3+ T cells was not different in SLE patients with high BAFF serum levels.

3.3.2. Association of BAFF and APRIL with Th1/Th2/Th17 cytokines in SLE patients

BAFF mainly correlates with serum levels of cytokines of the Th2 profile including IL-4 (r = 0.424, $p < 0.05$), IL-6 (r = 0.420, $p < 0.05$), IL-10 (r = 0.459, $p < 0.01$), whereas APRIL correlates with

Table 2
BAFF-R, TACI and soluble cytokine expression in SLE patients according to BAFF levels.

Expression profile		SLE		
		BAFF levels < 2 ng/mL n = 18	High BAFF levels ≥2 ng/mL n = 18	*p*
Receptors	BAFF-R (MFI)	2803.8 ± 1,397.2	2641.7 ± 782.0	0.937
	TACI (MFI)	2431.0 ± 904.5	2700.6 ± 877.1	0.179
B stimulator	APRIL*	22.33 ± 19.52	47.35 ± 29.37	0.038
Th1	IL-12	211.57 ± 226.61	313.38 ± 274.95	0.097
	IL-2	10.06 ± 14.75	22.56 ± 14.81	0.037
	IFN-γ	6.42 ± 0.99	7.76 ± 2.73	0.107
	TNF-α	21.45 ± 63.58	62.44 ± 153.52	0.149
Th2	IL-4	9.97 ± 23.05	20.30 ± 38.59	0.062
	IL-6	11.85 ± 15.00	34.92 ± 61.99	0.005
	IL-10	7.67 ± 2.74	14.54 ± 10.54	0.022
	IL-13	2.60 ± 11.06	7.37 ± 22.48	0.406
Th17	IL-1β	11.40 ± 27.05	25.69 ± 55.81	0.095
	IL-17	7.99 ± 10.16	12.94 ± 22.68	0.527

SLE: systemic lupus erythematosus; BAFF-R: B cell activation factor receptor, MFI: mean fluorescence intensity, TACI: Transmembrane activator and CAML interactor, APRIL: a proliferation-inducing ligand, IL-12: interleukin-12, IL-2: interleukin-2, IFN-γ: interferon gamma, TNF-α: tumor necrosis factor alpha, IL-4: interleukin-4, IL-6: interleukin-6, IL-10: interleukin-10, IL-13: interleukin-13, IL-1β: interleukin-1β, IL-17: interleukin-17.
Cytokines values are shown in pg/mL. APRIL* values are shown in ng/mL.
Data provided in mean ± standard deviation. Mann-Whitney *U* test.

Th1 profile IL-2 (r = 0.666, $p < 0.01$), IL-12 (r = 0.611, $p < 0.01$), TNF-α (r = 0.471, $p < 0.05$) and IL-1β (r = 0.422, $p < 0.05$) (Fig. 3). BAFF-R expression showed no association with any cytokine, while TACI expression correlates with IL-6 (r = 0.448, $p < 0.01$) and IL-10 serum levels (r = 0.417, $p < 0.05$) (data not shown).

3.4. Correlation of cytokines and receptors with disease activity index and organ damage index

Serum BAFF (r = 0.621, $p = 0.001$) and APRIL levels (r = 0.416, $p = 0.026$) correlate with disease activity (Fig. 4a and 4b, respectively). BAFF-R MFI on CD3+ T cells correlates inversely with the disease activity index (r = -0.538, $p = 0.001$), whereas the TACI percentage (r = 0.437, $p = 0.012$) and MFI (r = 0.530, $p = 0.001$) expression on CD3+ T cells correlates with Mex-SLEDAI (Fig. 4c). In addition, proinflammatory cytokines including IL-17 (r = 0.526, $p = 0.001$) and TNF-α (r = 0.410, $p = 0.013$) showed a positive correlation with the Mex-SLEDAI score (Fig. 4e and 4f). Furthermore, APRIL (Fig. 4d) also correlates with the damage organ index score (r = 0.477, $p = 0.01$). Other cytokines that showed positive correlations with SLICC score were IL-10 (r = 0.426, $p = 0.01$) and IFN-γ (r = 0.440, $p = 0.007$) (Fig. 4g and h).

3.5. Association of serum cytokine levels with autoantibodies

As shown in Fig. 5a, serum BAFF levels correlate with ANA titers (r = 0.567, $p = 0.006$), IL-4 (r = 0.442, $p = 0.035$) (Fig. 5b) and TNF-α (r = 0.526, $p = 0.010$) (Fig. 5c). In addition, the IL-10 levels were significantly higher among SLE patients positive for anti-La (SSB) antibodies (6.87 ± 1.36 vs 11.45 ± 8.38 pg/mL; $p < 0.05$) (Data not shown).

3.6. Expression of BAFF-R, TACI and systemic cytokines in SLE subsets.

Based on the SLEDAI score, patients were categorized into four groups as follows: inactive (Mex-SLEDAI ≤ 2) (n = 10), mild and moderate (Mex-SLEDAI 3–5) (n = 9), and severe activity (Mex-SLEDAI ≥ 6) (n = 12) who received standard-of-care therapy for their disease, and the treatment-naïve group (n = 5), which included newly diagnosed patients with severe disease activity who had not received prior steroid or immunosuppressive therapy.

Table 3 shown the values of each receptor and cytokine expression profile. BAFF-R expression was high on CD3+ T cells of inactive SLE patients compared to active patients and HC. In contrast, TACI expression was low on CD3+ T cells of inactive patients compared to active SLE patients. The cytokines APRIL (58.92 ± 24.58 ng/mL) and BAFF (8.70 ± 8.53 ng/mL) were higher in treatment-naïve patients compared with HC and SLE patients with current treatment and active disease (respectively) ($p < 0.05$).

Differences in all cytokines were found, except for IFN-γ and IL-1β. The Th1 cytokines IL-12 and IL-2 levels were increased in treatment-naïve compared with inactive patients ($p < 0.05$). TNF-α showed increased levels in treatment-naïve patients compared with inactive, mild-moderate and severe activity SLE groups ($p < 0.01$). The Th2 cytokines IL-4 and IL6 were increased in treatment-naïve compared with all SLE activity groups ($p < 0.01$), whereas IL-10 was slightly elevated in severe activity patients compared to inactive patients ($p < 0.05$). Finally, cytokine IL-17 was higher in the treatment-naïve patients compared to those inactive ($p < 0.05$).

Furthermore, patients with renal activity (58.49 ± 28.13 ng/mL) showed higher serum APRIL levels compared with those without renal activity (27.41 ± 22.19 ng/mL; $p < 0.05$), whereas BAFF was increased in patients with serous (11.22 ± 7.96 ng/mL) and articular (6.62 ± 7.83 ng/mL) manifestations compared with active SLE patients without those manifestations (2.28 ± 1.31 ng/mL; $p < 0.01$) and (2.57 ± 1.58 ng/mL; $p < 0.05$) respectively (Data not shown). Finally, increased APRIL levels in patients with chronic renal failure (CRF) (50.15 ± 20.39 ng/mL) compared to those unaffected (32.78 ± 18.64 ng/mL; $p < 0.048$) were found.

4. Discussion

SLE is a complex autoimmunity disease characterized by a loss of tolerance for self-antigens, which drives the production of pathogenic autoantibodies that are considered the hallmark of disease. Although factors that contribute to abnormal selection and maintenance of autoreactive cells are incompletely understood, the BAFF and APRIL cytokines have been related with autoimmune disease due to their relevant participation in the maturation and survival of B cells [36].

The BAFF function of CD4+ T cells cytokine production [37] through the BAFF-R receptor *in vitro* [38] and *in vivo* [31] has been poorly studied. However, a decreased frequency of activated and memory T cells has been shown following pharmacological blockade of BAFF, suggesting a regulatory role [39]. The aim of this work was to evaluate BAFF and APRIL associations with the receptors BAFF-R and TACI on CD3+ T cells and to evaluate the T helper cytokine profile in SLE patients.

Differences in BAFF-R and TACI expression on CD3+ T cells between SLE and healthy controls were not found; however, this is an exploratory study, so we cannot establish that there are no differences in other T subpopulations. When the data were assessed according disease activity, both receptors behave differently. BAFF-R MFI was increased on inactive SLE patients compared with active patients, who had similar levels to HC. A previous study by our group found that BAFF-R expression on B cells was lower in active SLE patients and correlates with disease activity [40], which suggests the possibility of complex regulatory mechanism of the receptor. Because BAFF could bind to naïve and primed/memory T cells and costimulate T cell activation [41], we hypothesized that BAFF increased serum levels observed in active patients and could induce regulation of BAFF-R expression in an effort to reduce cellular activation. The function of BAFF-R and TACI on T cells remains elusive; however, some research groups

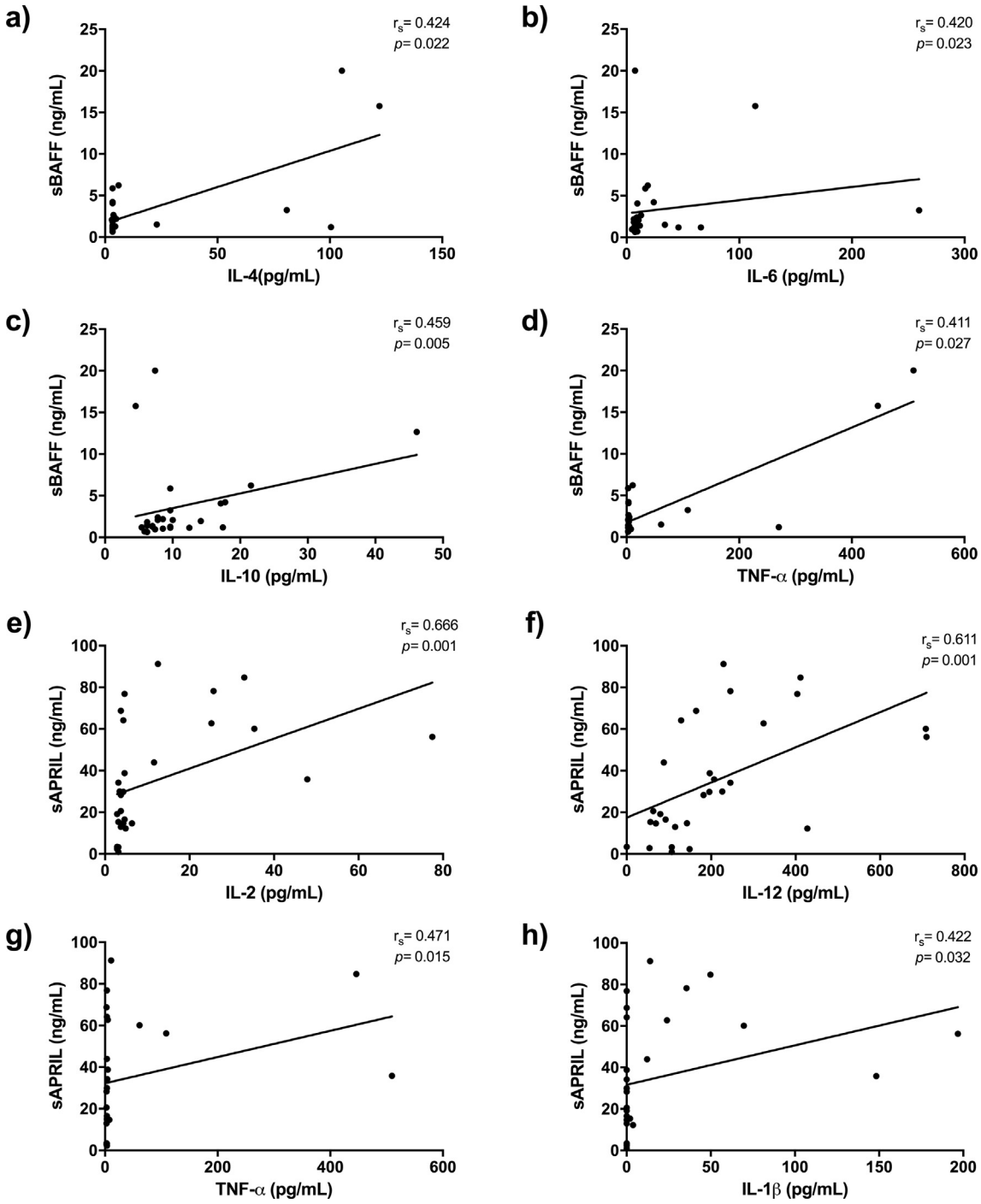

Fig. 3. Association of BAFF and APRIL with Thl/Th2/Thl7 cytokincs in SLE patients. r_s: Spearman's correlation coefficient; BAFF: B-cell activating factor, IL-4: interleukin (IL)-4, IL-6, IL-10, TNF-α: tumor necrosis factor alpha, APRIL: a proliferation-inducing ligand, 1L-2, 1L-I2, IL-β.

have made interesting findings. It recently was reported BAFF-R could be processed by ADAM10 and ADAM17 metalloproteases and be released in a soluble form to regulate the receptor surface levels on B cells. The remarkable finding of the mentioned study was that BAFF-R is processed in a regulated manner after BAFF binding, but only in B cells coexpressing TACI, which indicates a novel regulatory mechanism [42].

Furthermore, Coquery *et. al* found an increase BAFF-R expression CD4+ T and Tfh cells in SLE compared to HC, and the numbers of these cells expanded in proportion of BAFF and IFN-γ, which promotes the abnormal survival of autoreactive B cells and uncontrolled GC responses [26]. Coquery's findings highlight the participation of BAFF-R in regulating Tfh cell differentiation, which was not explored in our study.

Despite the evidence for TACI expression on activated T cells, its role in the regulation of T cell function is unknown. In this study of the TACI receptor, we found the opposite behavior of BAFF-R. While active SLE patients had increased TACI MFI expression, in the inactive SLE patients TACI MFI was similar to HC. Some studies demonstrated that diminished TACI expression could be beneficial in the autoimmunity context. It appears that soluble TACI-Fc blocks the activation of T cells *in vitro* and their administration in mice inhibit antigen-specific activation. In addition, the TACI-Fc treatment administered in a collagen-induced arthritis (CIA) mouse model inhibits collagen-specific B and T

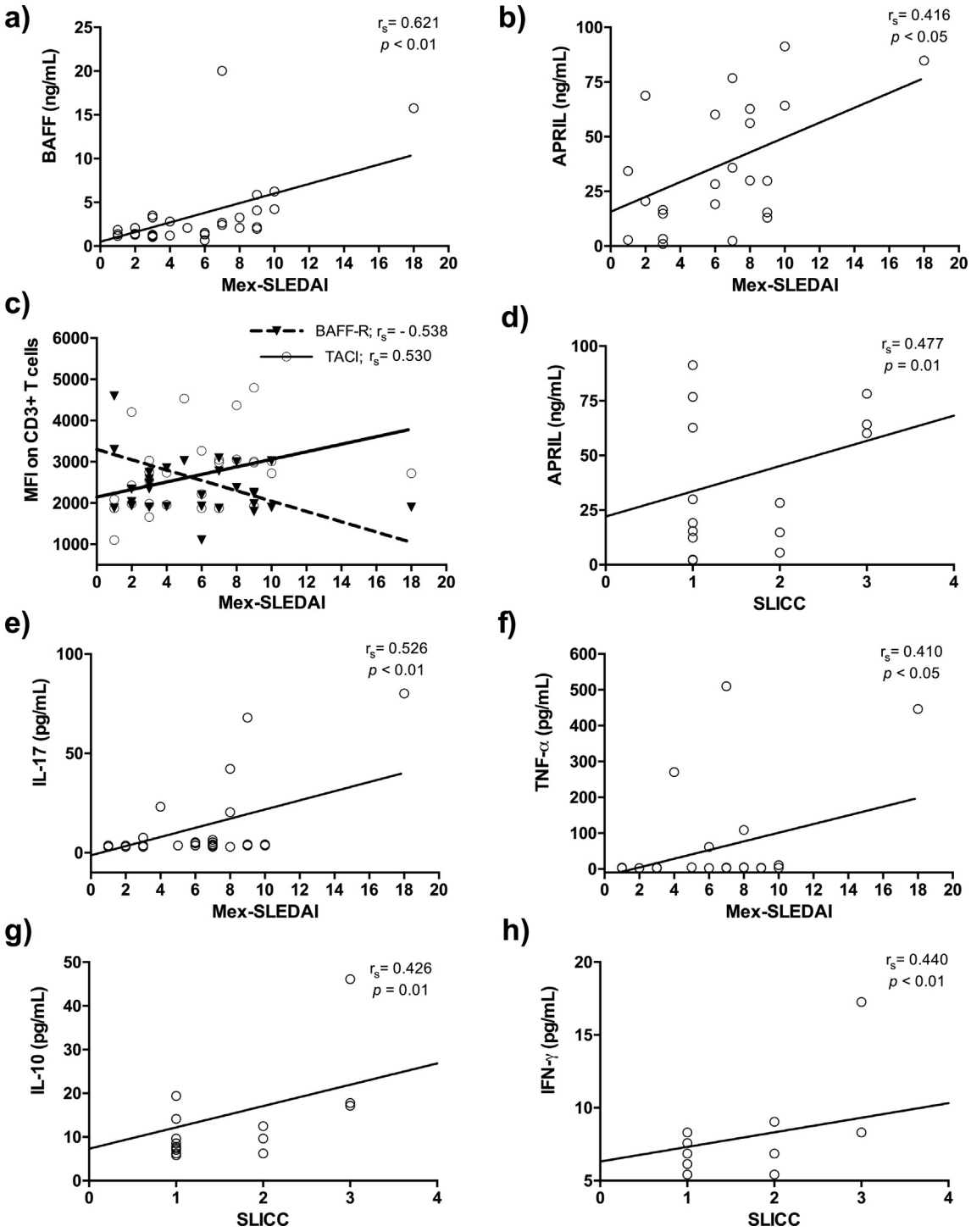

Fig. 4. Correlation between serum levels of cytokines and MFI BAFF-R and TACI receptor expression on CD3+ T cells with disease activity and damage score index. rs: Spearman's correlation coefficient, BAFF: B-cell activating factor, Mex-SLEDAI: Mexican version of the Systemic Lupus Erythematosus Disease Activity Index, APRIL: a proliferation-inducing ligand, MFI: mean fluorescence intensity, BAFF-R: B-cell activating factor receptor, TACI: Transmembrane activator and CAML interactor, SLICC: Systemic Lupus International Collaborating Clinics index, TNF-α: tumor necrosis factor alpha, IL-17: interleukin 17, 1L-10: interleukin 10, IFN-γ: interferon gamma.

cell responses, demonstrating the participation of TACI in the costimulatory T-B cell responses [43].

Regarding the B cell proliferation cytokines, the BAFF serum levels were higher in SLE patients, especially in the severe and naïve-treatment groups; this behavior in SLE has been reported by other authors [9,10,12,15,16] and in another diseases such as Sjogren's syndrome [44–46] and rheumatoid arthritis [47,48], suggesting that dysregulation of this cytokine could be involved in the pathogenesis of autoimmune diseases. In addition, BAFF levels correlated with disease activity in SLE patients, similar to the findings in of previous publications [10,11,40]. Nevertheless, controversy remains about the utility of serum BAFF as a disease activity biomarker, since another studies reported no association [9,12,49,50]. We found BAFF serum levels to correlate inversely with BAFF-R MFI on CD3+ T cells, as had been

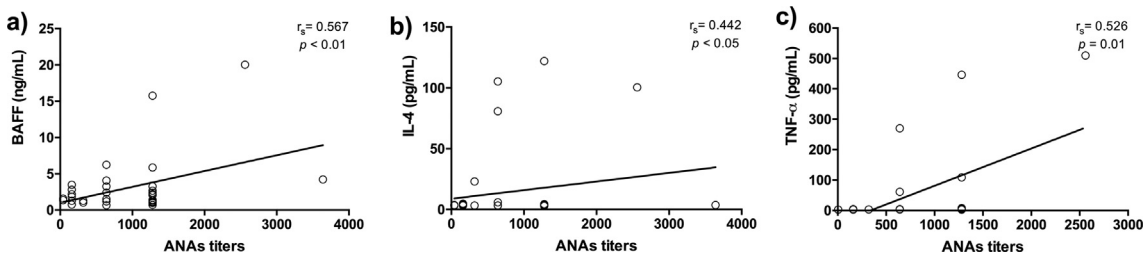

Fig. 5. Correlation between serum levels of cytokines with ANA titers. r_s: Spearman's correlation coefficient, BAFF: B-cell activating factor; ANA: antinuclear antibody, 1L-4: interleukin 4, TNF-α: tumor necrosis factor alpha.

Table 3
BAFF-R, TACI and soluble cytokine expression in SLE patients according to study groups.

Expression profile		HC n = 15	SLE			
			Inactive n = 10	Mild-moderate n = 9	Severe n = 12	*Treatment-naïve** n = 5
Receptors	BAFF-R (MFI)	2,210 ± 511	3,844 ± 1,506[a,b,c,d]	2,264 ± 340	2,269 ± 597	2,390 ± 515
	TACI (MFI)	2,114 ± 676[b,c]	1,868 ± 537[b,c,d]	2,475 ± 756[b]	2,922 ± 927[a]	3,268 ± 719[a]
B stimulator	APRIL*	12.72 ± 19.31	20.02 ± 18.44	24.97 ± 26.03	46.02 ± 28.54[a]	58.92 ± 24.58[a]
	BAFF*	0.95 ± 0.21	1.39 ± 0.58[b]	1.74 ± 0.86[b]	3.17 ± 1.98[b]	8.70 ± 8.53[a]
Th1	IL-12	94.60 ± 41.84	132.13 ± 76.51[b]	256.12 ± 262.09	264.96 ± 206.17	528.65 ± 405.2[a]
	IL-2	3.96 ± 1.01	5.23 ± 2.97[b]	12.28 ± 18.46[b]	8.90 ± 10.62	63.52 ± 74.19[a]
	IFN-γ	5.61 ± 0.63	6.35 ± 0.68	6.86 ± 1.40	7.86 ± 3.31	7.58 ± 1.44
	TNF-α	2.98 ± 0.50	3.64 ± 1.57[b]	33.00 ± 26.03[b]	86.38 ± 168.22[a,b]	214.63 ± 245.1[a]
Th2	IL-4	3.53 ± 0.24	3.69 ± 0.51[b]	14.27 ± 32.32[b]	5.29 ± 5.63[b]	63.21 ± 56.07 [a]
	IL-6	6.20 ± 12.35	6.42 ± 1.79[b]	18.80 ± 21.69[b]	17.08 ± 13.44[b]	80.71 ± 109.77[a]
	IL-10	5.77 ± 0.40	6.60 ± 0.71[c]	10.20 ± 5.52	11.30 ± 6.66[a]	15.46 ± 11.97
	IL-13	0.14 ± 0.20	0.00 ± 0.00[b]	5.21 ± 15.65	0.00 ± 0.00[b]	26.55 ± 38.87[a]
Th17	IL-1β	0.15 ± 0.6	2.84 ± 6.07	13.68 ± 31.60	10.10 ± 21.51	78.98 ± 89.47
	IL-17	3.10 ± 0.24	5.20 ± 4.62[b]	10.85 ± 13.35	15.00 ± 23.59	23.17 ± 32.57[a]

SLE: systemic lupus erythematosus; BAFF-R: B cell activation factor receptor, MFI: mean fluorescence intensity, TACI: Transmembrane activator and CAML interactor, APRIL: a proliferation-inducing ligand, IL-12: interleukin-12, IL-2: interleukin-2, IFN- γ: interferon gamma, TNF- α: tumor necrosis factor alpha, IL-4: interleukin-4, IL-6: interleukin-6, IL-10: interleukin-10, IL-13: interleukin-13, IL-1β: interleukin-1β, IL-17: interleukin-17.
Cytokines values are shown in pg/mL. APRIL* and BAFF* values are shown in ng/mL.
Data provided in mean ± standard deviation. Two-tailed Kruskal–Wallis, Dunńs test as pos-hoc.
* Treatment-naïve patients included newly diagnosed patients who had not received prior steroid or immunosuppressive therapy.
[a] $p < 0.05$: significance vs HC.
[b] $p < 0.05$: significance vs treatment-naïve patients.
[c] $p < 0.05$: significance vs severe patients.
[d] $p < 0.05$: significance vs mild-moderate patients.

previously reported on CD19+ B cells of SLE patients [23].

Furthermore, BAFF level associations with clinical manifestations are strongly related, as shown by a study conducted by Petri *et al.* in which, using multivariate analysis, it was determined that serum concentrations greater than two nanograms (≥2 ng/mL) could predict peaks of reactivation of moderate to severe disease in patients with SLE treated with standard pharmacological therapy [51]. It should be note that the discrepancy between the results in the different studies could be attributed to various factors, including the methodological design of the studies, methodology used and sensitivity of the assays, in addition to the genetic characteristics of the populations studied. Regarding this last point, it should be remembered that susceptibility to a complex pathology such as SLE has been associated with ethnic variation, where African, Asian and Latino subjects suffer more severe conditions of the disease compared with Caucasian patients [52,53]. In this context, a study reported that African-American patients have higher levels of serum BAFF than Caucasian patients; however, the same study indicates that the increase in serum concentration is associated with the increase in the SLEDAI index only in white patients and not in African-Americans. This finding emphasizes that it is necessary to study the variability among ethnic groups, because these factors can contribute to the susceptibility of the disease, in addition to promoting the understanding of the biology of this cytokine.

Another molecule that participates in the homeostasis of B cells, the APRIL cytokine, was analyzed due to its homology with BAFF and because it shares binding with two receptors (TACI and BCMA). The serum levels of APRIL were elevated in patients with SLE compared to HC, and this increase was greater in patients with severe activity with respect to inactive patients and HC, in addition to correlating with disease activity and with the SLICC damage index. Previous reports have shown the association of soluble levels of this cytokine with the activity of the disease, specifically, musculoskeletal manifestations [15–18], neurolupus [54] and lupus nephritis [55]. This result suggests that APRIL could be an important marker of disease activity, as well as of prognosis in patients with SLE; however, it also highlights the need to elucidate the role of APRIL in autoimmune diseases to improve its therapeutic approach. The APRIL murine knockout model shows a normal phenotype, but after being studied separately by another group of researchers, it was found that the model shows deterioration in the ability to produce type A immunoglobulins (IgA) and therefore, the low levels in serum and mucous membranes [56,57] decrease the mouse immunological response capacity. Another study showed that both BAFF and APRIL can promote T- independent change of isotype through binding to TACI [58], favoring the production of high affinity antibodies. The pharmacological blockade of BAFF and APRIL with a fusion protein called atacicept (TACI-Fc) was associated with a severe decrease of immunoglobulins and the appearance of severe infections in patients with lupus nephritis [59].

In our study, we observed that patients with renal activity had higher serum levels of APRIL. Although it should be considered that this study has a reduced number of patients, the association between high levels of APRIL and renal activity are strong. Among the manifestations of SLE, renal is one of the most common and is a cause of significant morbidity and mortality [60]; therefore, biomarkers to detect lupus nephritis would improve treatment and prevent irreversible damage to the kidney. As previously mentioned, one study reports a correlation between renal activity and serum levels of APRIL in patients with lupus nephritis, in addition to finding that patients not responding to conventional therapy maintained higher levels of APRIL [55]. For this phenomenon, in which the concentration of the cytokine might be associated with tissue-specific damage, it is necessary to take into account the ability of APRIL to bind to HSPG [61] and to create a concentrated reservoir of the ligand in organs, including the kidney, so it is necessary to investigate the expression of this cytokine at the tissue level. In the murine nephropathy model, the blockade of APRIL diminished the nephritogenic IgA levels and proteinuria [62]. In this study, we found that TACI expression on CD3+ T cells correlates with IL-10 in SLE patients, and IL-10 and APRIL were increased in active SLE patients; we cannot probe this association, but several reports appear to confirm the relationship of APRIL and IL-10 through TACI. APRIL drives TACI-mediated switching from IgA1 to IgA2 through the Toll-like receptor (TLR) [63] and induces the nuclear factor of activated T-cell (NFAT), transcriptional factor critical for the IL-10 production [64]. Furthermore, APRIL promotes through TACI the expression of IL-10, Foxp3, CTLA-4, TGFβ, and this finding suggests that TACI might directly regulate the immune suppressive function of Tregs [65].

Cytokines are soluble factors that participate in the differentiation, maturation and activation of various cells of the immune system. Cytokines are involved in immune dysregulation and also in the local inflammatory response, which leads to tissue damage [4]. SLE has been described as a disease polarized towards the Th2 profile [66]. IL-4 and IL-6 were elevated in SLE as previously reported [67,68]. Recently, it was reported that IL-4 acts with BAFF in synergy to stimulate the maturation of B cells and the resistance to apoptosis in activated B cells [69], whereas IL-6 and TGF-β together with IL-21 [70] and BAFF promote the activation of the transcriptional factor RORγt, through STAT3, favoring differentiation and expansion of the Th17 phenotype [71]. The IL-17 cytokine was increased in treatment-naïve patients and correlates with disease activity, as observed in others reports [72–74]. The serum levels of IFN-γ correlated with the damage index in SLE patients, and it should be noted that this cytokine has been associated with kidney damage and increased activity in lupus [75] in addition to being a cytokine that could increase the secretion of factors of survival and differentiation of B cells such as BAFF and APRIL, feeding back the survival of autoreactive cells and the increase of autoantibody titers [76,77]. Another cytokine that has been found promote BAFF synthesis in a dose-response manner is IL-2 [78], which was also associated with BAFF increased serum levels in our SLE patients.

In agreement with our data, researchers reported that patients with SLE have increased soluble levels of IL-10 [68,79], and the cells of these patients produce a greater amount of the cytokine [80–82]. In addition, the increase in its production is associated with an increase in the activity of the disease [68,83]. This cytokine contributes to the alteration of B cells in SLE patients, including the expansion of plasma cells in the periphery, and increases the production of antibodies [84]. It has been suggested that the hyperactivity observed in B-lymphocytes of patients with SLE might be the result of autocrine and paracrine effects of IL-10 [85]. The expression of IL-10 has been detected in kidney cells of patients with SLE [86]; in our study we found that serum levels of IL-10 are associated with the rate of damage in patients, which expands upon the evidence that the deregulation of this cytokine could directly contribute to the pathogenesis of the disease. Other researchers have reported the increase in transcripts of IL10 in PMBC of patients with LEG [87,88], and this molecule could be used as a biomarker.

Several mechanisms can contribute to the increase of IL-10 observed in SLE patients as levels of proinflammatory cytokines (IFN-γ and TNF-α); in this sense, the polarization towards a proinflammatory profile in the medium could allow an imbalance in the signaling mediated by the TNFR receptor, increasing even the synthesis of IL-10 [89,90] in various cells. The signaling pathways activated by BAFF-R and TACI have been poorly characterized. Like other members of the TNF superfamily, these receptors can bind to TRAF proteins and activate the transcription of NF-κB and JNK protein kinase. It is documented that the antiapoptotic action of BAFF through BAFF-R occurs as consequence of the non-canonical pathway of NF-κB activation; however, BAFF increases the interaction of TRAF3 and BAFF-R, also activating the classical NF-κB pathway and thus increasing the expression of IL-10 in B cells [91], suggesting a feedback on these cytokines that allows the survival and maturation of B lymphocytes and antibody production. Additionally, in CpG-ODN peripheral blood B cells, BAFF stimulation significantly increased IL-10 and IL-6 production, indicating that experienced cells could respond differently to T-cell independent B-cell class switch inducing factors [92].

The fact that SLE patients maintain high levels of BAFF, regardless of therapy, and the association of this cytokine with autoantibody titers reflects the hyperactivity of the immune system, which translates to vulnerability to relapses. The net effect observed is high BAFF signature SLE patients maintain elevated levels of APRIL, IL,2, IL-6 and IL-10, which might be favoring a feedback cycle in patients with SLE, contributing to the perpetuation of inflammatory response.

5. Conclusions

In patients with SLE, organ damage occurs because of the chronic autoimmune response, developed because of the loss of immunological tolerance and the failure of regulatory mechanisms. Due to unknown factors, in both cases, the target organ and the immune system activate an inflammatory response that causes organic damage that leads to the clinical manifestations of this disease.

This study demonstrates an imbalance in the Th1/ Th2 cytokine profile, with increased BAFF and APRIL levels. Environment polarization produced during an immune response to autoantigens plays a key role in maintaining and exacerbating the autoimmune response. In this context, the BAFF/APRIL system has outstanding participation. BAFF and APRIL could orchestrate the activation and differentiation of B cells, contributing to modulation of the microenvironment through the costimulation of BAFF-R and TACI receptors expressed on T cells.

The dynamic nature of cytokines and the fact that they could constitute self-regulatory networks is a point to consider in studies such as the present. We consider important a future analysis of the coexpression of these molecules at the transcriptional and membrane level at local tissue, in addition to the signaling pathways that could help to elucidate the regulatory mechanisms of BAFF/APRIL system receptors in a disease as complex as systemic lupus erythematosus.

The participation of BAFF-R and TACI in T cell activation remains elusive, and efforts to explain the contribution of these in the SLE context could help reveal new mechanisms that can potentially be exploited to develop novel therapeutic strategies in autoimmunity.

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Conflict of interest

The authors disclose no financial conflicts of interest in connection with this study.

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