Ying-Yang (YY-1) Expression and Fas in Biopsies of Children With Type IV Lupus Nephritis Correlates With the Clinical Condition

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Background: It has been demonstrated that Fas-mediated apoptosis participates in the physiopathology of lupus nephritis, although it is not clear whether it contributes to the development of the tissue damage. Since YY-1 down regulates Fas in cancer cell lines, it is reasonable to consider that this transcription factor may control Fas expression in lupus nephritis. The objective was to determine the correlation between YY-1 and Fas expression in renal biopsies from children with type IV lupus nephritis, and their association with the clinical condition of the patients.
Material and methods: Eighteen biopsies from children with type IV lupus nephritis and 5 controls were studied. Fas and YY-1 expression were determined by immunochemistry and quantified by densitometry analysis. The clinical conditions at the moment the biopsy were obtained from the clinical records and the results were analyzed through a one-way ANOVA with $P<.005$.
Results: The results of the densitometry analysis showed an inverse relationship between YY-1 and Fas expression. YY-1 was grouped according to the intensity of expression in low, moderate and high and compared with the expression of Fas. The lupus nephritis biopsies, which revealed high expression of YY-1, corresponded to patients with less number of clinical complications, better outcome, and fewer alterations on renal function.
In contrast, low expression of YY-1 correlated with high Fas expression and worst clinical conditions.
Conclusions: The present study suggests that YY-1 regulates Fas expression in lupus nephritis and that it is associated with the clinical outcome of the patients, although further studies are necessary to determine weather it factor may serve as a prognosis factor. This is the first evidence of YY-1 participation in the physiopathology of lupus nephritis.

Key words: Lupus nephritis. Transcription factor YY-1. Fas. Apoptosis.

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La expresión de Yin-Yang-1 (YY-1) y Fas en las biopsias de niños con nefritis lúpica tipo IV se correlaciona con la condición clínica

Antecedentes: La apoptosis mediada por Fas participa en la fisiopatología de la nefritis lúpica. Debido a que YY-1 regula negativamente el Fas en líneas celulares de cáncer, es razonable considerar que este factor de transcripción pueda controlar la expresión de Fas en la nefritis lúpica. El objetivo es determinar la correlación de la expresión de YY-1 y Fas en biopsias de niños con nefritis lúpica de tipo IV y su asociación con la condición clínica de los pacientes.
Material y métodos: Se estudiaron 18 biopsias de niños con nefritis lúpica de tipo IV y 5 controles. La expresión de Fas y YY-1 se determinó mediante inmunohistoquímica y se cuantificó mediante análisis densitométrico.
Se obtuvo información sobre el estado clínico de los pacientes en el momento de la biopsia a partir de los expedientes, y los resultados se analizaron mediante ANOVA de una vía. Se consideró significativo un valor $p < 0,005$.
Resultados: Los resultados del análisis densitométrico muestran una relación inversa entre la expresión de YY-1 y Fas. Se agrupó YY-1, de acuerdo con la intensidad de su expresión, en baja, moderada y alta para poder compararla con la expresión de Fas. Las biopsias de nefritis lúpica que mostraron alta expresión de YY-1 correspondieron a pacientes con menor número de complicaciones clínicas, mejor desenlace y menor número de alteraciones en la función renal. En

contraste, la expresión de YY-1 baja se correlacionó con alta expresión de Fas y peores condiciones clínicas.
Conclusiones: En conclusión, el presente estudio indica que YY-1 regula la expresión de Fas en la nefritis lúpica y que se encuentra asociada con el desenlace clínico de los pacientes, si bien son necesarios más estudios para determinar si puede servir como marcador pronóstico. Hasta donde sabemos, ésta es la primera evidencia de que YY-1 participa en la fisiopatología de la nefritis lúpica.

Palabras clave: Nefritis lúpica. Factor de transcripción YY-1. Fas. Apoptosis.

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic, episodic autoinmune disease characterized by the inflammation of blood vessels and connective tissue, as well as by the presence of antinuclear (ANA) and anti-DNA antibodies. Its clinical manifestations are extremely variable and its course is progressive.[1] One of the common and severe manifestations is kidney damage (65%-85%), because it is associated with complications that can lead to death especially in patients with childhood-onset SLE.[2] Several histological forms of lupus nephritis have been determined and the most common classification is the one proposed by the WHO, being its most severe for type IV.[3]

It has been shown that diverse autoimmune diseases course with an increase in programmed cell death (apoptosis). Apoptosis is activated by receptors for cell stress and is regulated by molecules such as Bcl-2/BclxL, FLIP, and IAP, as by extracellular survival factors. The expression of lethal factors such as TNF and FasL has been noted in glomerular damage,[4] as well as an increase in the expression of Fas, Bcl-2, and Bax in proliferative glomerulonephritis in humans.[5] Apoptosis contributes to the remodelation and recovery of tissue structure.

Some experimental models point out that apoptosis coexists with renal cell proliferation.[4] On the other hand, it has been proposed that apoptosis favors a resolution in glomerular damage, but can also contribute to the progress of renal disease and eventually to the development of sclerotic hypocelullar glomerular aplasia.[6] Studies have been carried out to determine the histological localization of the cells undergoing apoptosis; Stollar et al[7] reported the accumulation of apoptotic cells in the germinal follicles of patients with SLE. Makino et al[8] carried out a stucdy in 22 patients with lupus nephritis and found 93% of apoptosis in patients with type IV glomerulonephritis. The percentage of apoptosis in the glomeruli correlated significantly with the serologic activity of lupus, anti-DNA antibodies, and complement. In contrast, in another study that evaluated the percentage of apoptosis in 25 biopsies of patients with type IV lupus nephritis and other gliomerulonephritis, it was found that patients with lupus nephritis had a lower percentage of apoptosis, which had a negative correlation with creatinine clearance. The authors concluded that apoptosis is reduced in said illness and that this mechanism leads to chronic renal damage.[9] In a study by Kirim et al,[10] the relationship between the clinical course and apoptosis in renal biopsies of lupus nephritis was investigated; a correlation between the nuclear cells of the renal biopsy and the activity index of lupus nephritis was found. The authors concluded that apoptosis can be a prognostic indicator in this nephropathy.

Diverse studies demonstrate the importance that Fas has in the pathogeny of lupus nephritis. However, it is unknown which factors regulate its expression during the development of this illness. YY-1 is a transcription factor that participates in the positive and negative regulation of diverse genes in mammals.[11] It has been demonstrated that YY-1 represses the transcription of the Fas gene by binding to a silencer region on its promoter.

Overexpression of Fas induces a sensitization of tumor-cell lines to apoptosis mediated by this receptor.[12] The participation of YY-1 has not been communicated until now in the phisiopathology of lupus nephritis, so in this study we evaluated whether YY-1 could be related to the expression of Fas and, therefore, had any participation in the pathogeny of lupus nephritis.

Material and Method

Samples

Eighteen biopsies from pediatric male and female patients, aged 6 to 15 years of age, with type IV lupus nephritis confirmed by a pathologist from the same hospital who was an expert in kidney tissue, protocolized by the department of pediatric rheumatology and filed in the department of pathology of the Hospital CMN La Raza, IMSS. Five kidney biopsies from pediatric patients without any lesions were also included. The protocol was approved by the research committee of the Hospital General del CMN La Raza (project no. R-2006-3502-6, I.P. Dra Sara Huerta Yepez).

Inmunohistochemistry

Fas and YY-1 determination was done through histochemistry. With the intention of reducing the variations between experiments, the reaction for each marker was done at the same time in all groups.

Cuts were mounted on slides covered with silane. They were maintained in a bacteriologic oven at 62°C for 45 min, to deparaffinate, with the following process.

The samples were hydrated: 3 baths immersions in xylene, lasting 8 minutes, 2 immersions in 100% ethanol, 1 immersion in 90% ethanol, 1 immersion in 70% ethanol, and 1 in distilled water, each one for 5 minutes.

Antigen recovery was carried out with sodium citrate, boiling for 20 min and with subsequent immersions to eliminate the sodium citrate. Endogenous peroxidase activity was eliminated with methanol and 3% hydrogen peroxide, twice for 15 minutes. Non immune binding of antibodies to tissue was eliminated by submersion for 60 min in 2% normal pig serum. Afterwards, sections were incubated over-night at room temperature in humid chambers with anti-YY-1 (Santa Cruz, CA, United Stets) 1:250 and anti-Fas antibodies (Santa Cruz, CA. United States) 1:1.000. They were later incubated with the second Biotin link (DAKO) antibody, with streptavidine conjugated with radish peroxidase (HPR); finally, color was generated through the addition of DAB (dyaminobenzidine) substrate for 3 min and 30 s; the reaction was stopped with tap water and counterstained with hematoxyllin 15 s. After that, the tissue was dehydrated with the following scheme: distilled water, 70% ethanol, 90% ethanol, 100% ethanol, and xylene in 5 minute-immersions each. Finally, preparations were covered with resin and let dry at room temperature.

Densitometry Analysis

Slides were analyzed on a microscope (Olimpus, BX-40), and the intensity of the immunostaining (Brown color) was quantified in 4 randomly chose fields, using an image analyzer with the Imagen-Pro® Plus software (Media Cybernetics,® Silver Spring, MD, United States).

TABLE 1. General Characteristics of Patients and Their Clinical Course During the Renal Biopsy Study*

Number	Hystopathological Classification	Age	Gender	Time Since Onset of Symptoms, Months	CRI	Clinical Course	RF
1	IV C	13	F	>6		Hypertensive crises	IRC
2	IV C	14	F	1		Normal	
3	IV C	14	F	>6		Normal	
4	IV C	15	F	>6		Normal	
5	IV B	14	F	2	Yes	Uremic syndrome/varicella	Normal
6	IV C	15	M	3		Hypovolemic shock/ hematologic SLE	Normal
7	IV C	14	F	2	Yes	Uremic syndrome, peritonitis, metabolic alterations, hemodyalisis	Normal
8	IV C	14	F	3		Vascular purpura	Normal
9	IV C	14	F	1		UTI due to *Staphilococcus* coagulase negative	Normal
10	IV B	14	M	2		Normal	
11	IV C	10	F	>6		Normal	
12	IV C	14	F	>6		Normal	
13	IV C	12	F	2		Normal	
14	IV C	13	F	1		Normal	
15	IV C	12	F	2		Severe pericardial effusion	Normal
16	IV C	6	F	4		Normal	
17	IV C	12	M	3		Normal	
18	IV C	12	F	>6		Normal	

*RF indicates renal function after 5 years (normal, creatinine <1 and normal uranalysis, and urinary sediment); CRI, chronic renal insufficiency; UTI, urinary tract infection; SLE, systemic lupus erythematosus; F, female; M, male.

Statistical Analysis

A database was elaborated and the information processed using the statistical software package Prisma® (GraphPad Software, Inc., San Diego, CA, USA).
Data was presented as arithmetical means for each group and standard deviations. The evaluation of differences in the number of positive cells and the density of the expression of immunohistochemical reactions was done using one-way ANOVA. A Tukey multiple comparison analysis to identify differences between groups was done, with a level of significance of P=.05.

Results

Clinical Analysis

Files of children with a diagnosis of SLE according to the classification criteria proposed by the American College of Rheumatology and renal affection, for which a biopsy had been carried out, were reviewed. We included 18 biopsies with type IV lupus nephritis, according to the morphological classification proposed by WHO. Regarding distribution by gender, 15 (84%) were female and 3 (16%) male. Mean age was 12.8 (interval, 6-15) years.
Clinical characteristics are shown in Tables 1 and 2. For evaluation purposes, our study population was divided into 2 groups, according to YY-1 expression. Group 1 included low to medium YY-1 expression and group 2, high expression. In group 1, which included 11 patients, 72.7% had microscopic hematuria, 63.6% had proteinuria (1-2 g/24 h), 45.4% had nephrotic syndrome and 91% had a creatinine clearance <50 mL/min/1.73 m^2 BSA; at the same time, 63.6% of patients had low complement levels and hyperazoemia. Two patients in this group presented with uremic syndrome that required dialysis and in a third patient, chronic renal failure ensued.
Of the group with high YY-1 (7 patients), 100% presented microhematuria, 42.8% proteinuria of 1-2 g/24 h, 57% had a creatinine clearance <50 mL/min/1.73 m^2 sc, 42% had low complement, and 14% hyperazoemia. None manifested acute renal failure or nephrotic syndrome.

TABLE 2. Clinical Behavior of Children With Type IV Lupus Nephritis, at the Moment of the Kidney Biopsy

Laboratory Alterations	YY-1 Low-Medium (n=11)	High YY-1 (n=7)	Total (n=18)
Active urinary sediment	11 (100%)	7 (100%)	100%
Microhematuria	8 (72.7%)	7 (100%)	83.3%
Macrohematuria	3 (27.2%)	0	16.6%
Proteinuria <1 g/24 h	1 (9%)	2 (28.5%)	16.6%
Proteinuria 1-2 g/24 h	7 (63.6%)	3 (42.8%)	55.5%
Proteinuria >3 g/24 h	2 (18%)	2 (28.5%)	22.2%
Hypertension	6 (54.5%)	4 (57.1%)	55.5%
Nephrotic/nephritic syndrome	5 (45.4%)	0	27.7%
Creatinine clearance <50 mL/min/1.73 m^2 sc	10 (91%)	4 (57.1%)	77.7%
Anemia	7 (63.6%)	7 (100%)	77.7%
Leukocytopenia	5 (45.4%)	3 (42.8%)	44.4%
Linphocytopenia	6 (54.5%)	4 (57.1%)	55.5%
Trombocytopenia	4 (36.3%)	4 (57.1%)	44.4%
Low C3 (80-120), C4 (18-25)	7 (63.6%)	3 (42.8%)	55.5%
Hyperazoemia	7 (63.6%)	1 (14%)	44.4%

Inmunohistochemical Findings

YY-1 was found (80%-90% of positive cells) mainly in the proximal and distal convoluted tubes, both in the cortex and medulla of the kidney (Figures 1-3). In the healthy controls, expression was found in the same sites (Figure 1). YY-1 was mainly expressed in the distal tubular epithelium, with variable degrees of intensity with relation to the cellular proliferation, with a low expression (1%-30%), medium (31%-70%), and high (71%-100%, Figures 2E and 2F). The expression of this protein in the glomeruli was <30% with respect to the expression of Fas. Regarding Fas immunostaining, it was found mainly in the proximal and distal convoluted tubes both in the cortex as in the medulla of the kidney (90% of positive cells) (Figures 1-3).
Healthy renal controls had expression in the same sites (Figure 1), though clearly less that in patients with nephritis. Staining of the apical membrane and cytoplasm of the cells of the proximal convoluted tubes was seen (Figures 1D, 3C, and 3D). In some lesions, the basal membrane of the distal convoluted tubes presented a higher intensity of expression. In the glomerulus, lesions with more cell proliferation stained positively for Fas, its distribution was larger in the mesangial cells and in Bowmans' capsule parietal cells, as in the mesangial matrix (Figures 1B, 3E, 3F).

Densitometry Analysis of Immunohistochemical Findings

Densitometry analysis of staining for Fas and YY-1 allowed for the elaboration of density expression graphs, processed

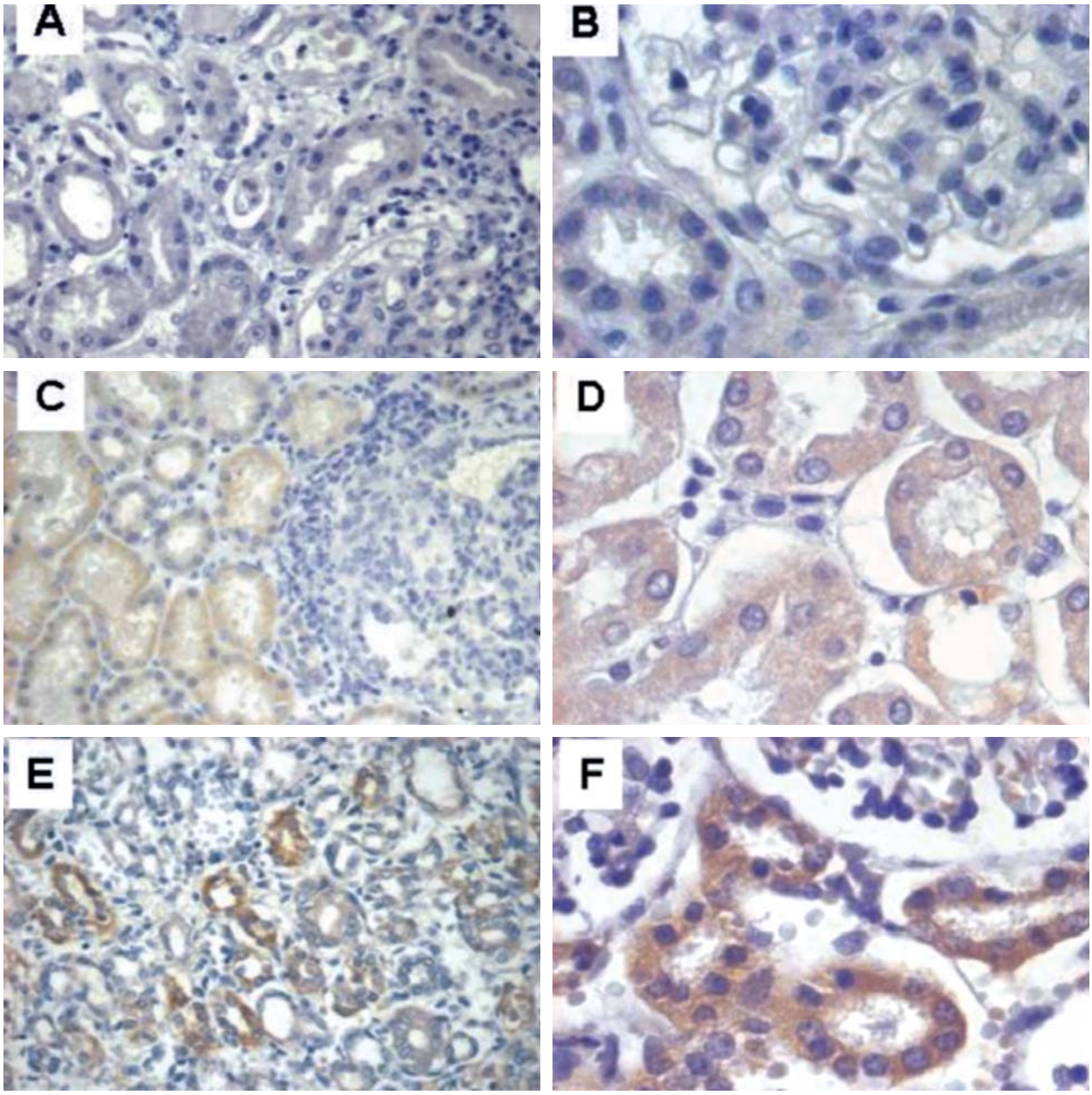

Figure 1. *Immunostaining of normal kidney tissue. A: negative controlwithout antibodies (×40). B: ×100. C: moderate expression of Fas in the proximal and distal convoluted tubules (×40). D: moderate expression of Fas is seen in the cytoplasm and membrane of the proximal convolute tubules (×100). E: intense expression of YY-1 in proximal convoluted tubules (×40). F: at larger magnification (×100) an intense expression of YY-1 in the cytoplasm of proximal convoluted tubes can be seen.*

using the Prisma® statistical analysis software. In Figure 4 the density of expression of YY-1 and Fas was shown in the renal tubules of samples with lupus nephritis and controls. Densitometry showed an inversely proportional relationship between the expression of YY-1 and Fas (P<.037). YY-1 and Fas expression in the glomeruli do not reveal significant differences (data not shown).

In Figure 5 the density of expression of YY-1 and Fas is shown and a comparison of the expression of these 2 proteins in all analyzed cases, grouping YY-1 according to the intensity of expression is low (less than 30% of positive cells), medium (31%-70%) and high (71%-100%), observing an inverse relation that reveals high YY-1 and low Fas (last columns) (P<.0003).

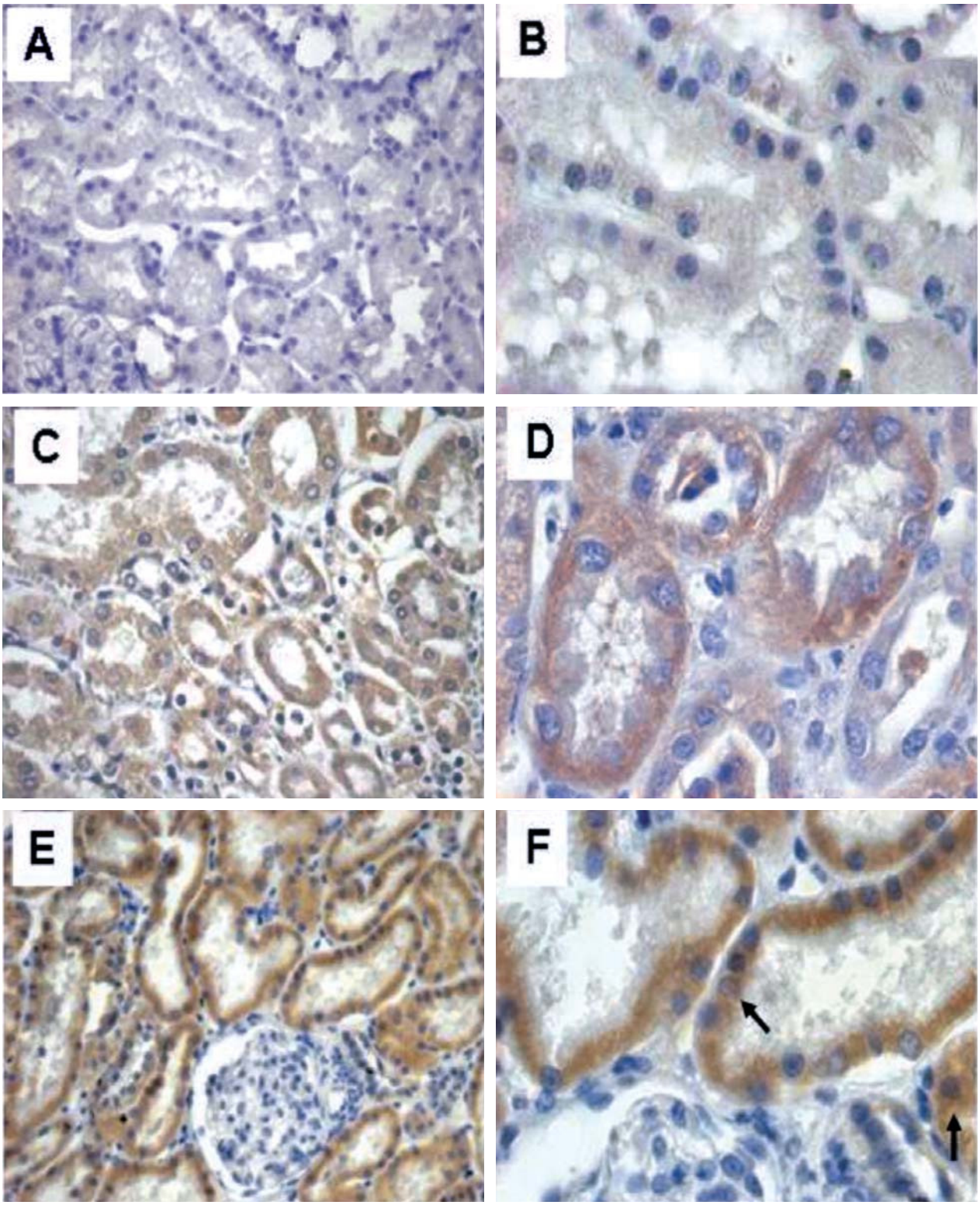

Figure 2. *Immunostaining of tissue withtype IV lupus nephritis with a low expression of Fas and a high expression of YY-1. A: negative control (×40). B: ×100. C: moderate expression of fas in the proximal and distal convoluted tubes (×40). D: a moderate expression of Fas in the cytoplasm and cell membrane of the proximal convoluted tubes (×100). E: intense expression of YY-1 in proximal and distal convoluted tubes, negative in the glomeruli (×40). F: intense expression of YY-1 in the cytoplasm of distal convoluted tubes; some positive nuclei can be observed (arrows), indicating activity of transcription factors; negative glomeruli (×100).*

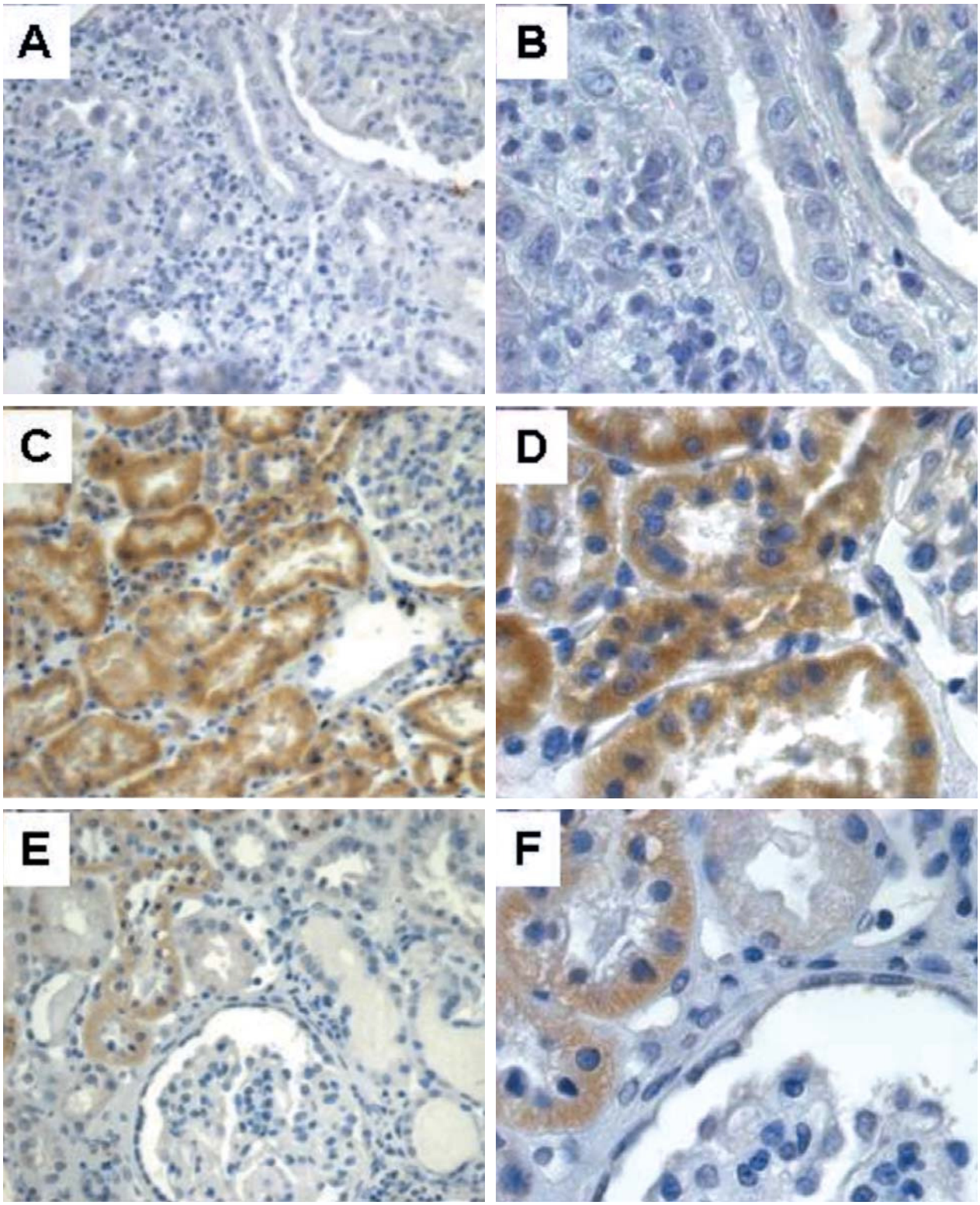

Figure 3. *Immunostaining of type IV lupus nephritis tissue with a high expression of Fas and a low expression of YY-1. A: negative control (×40). B: ×100. C: intense expression of Fas in the proximal and distal convoluted tubes, negative in the glomeruli (×40). D: same patient, intense expression of Fas in the cytoplasm and membrane of the proximal convoluted tubes (×100). E: low expression of YY-1 in distal tubules (×40). F: at larger magnification (×100) a low expression, mainly in the cytoplasm of the distal convoluted tubules is shown; negative glomeruli can be seen.*

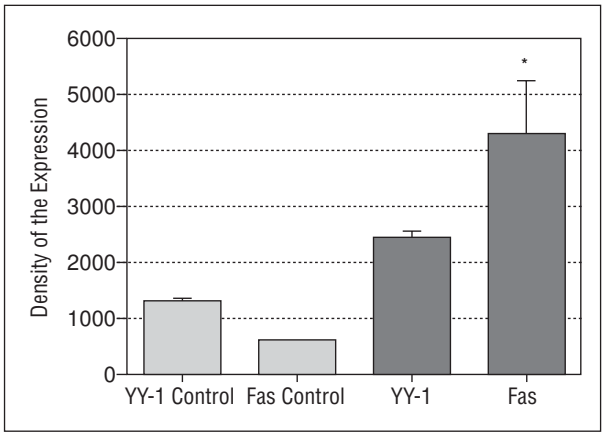

Figure 4. *Density of the YY-1 expression compared to Fas in the tubules of biopsies and healthy controls. The density of expression was determined in 4 different fields of the slide selected randomly, obtaining a mean for each patient.*
Bars represent the arithmetic mean by group and the standard deviation, observing a significant increase in the expression of Fas that is inversely related to YY-1 in lupus nephritis biopsies and inversely proportional in healthy controls (P<.037).

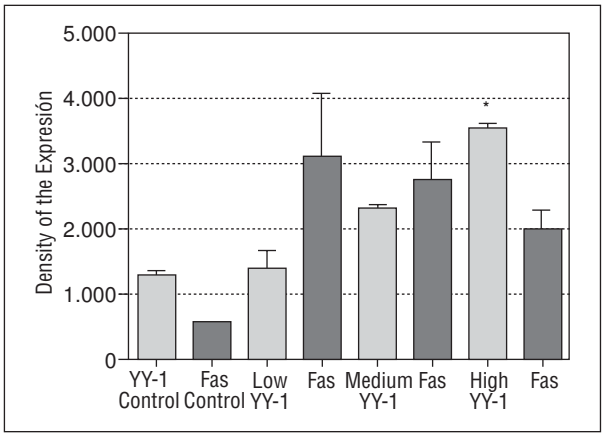

Figure 5. *The graph shows the presence of YY-1 when grouped by density of expression in low, medium, and high with respect to the expression of Fas (of each patient) in the tubules of biopsies and healthy controls. The density of expression was determined in 4 different fields selected randomly in each slide, obtaining a mean in each patient. Bars represent the arithmetical mean by group and standard deviation. An inversely proportional distribution is observed, when comparing the expression of YY-1 with Fas. Note that in the last 2 bars, when YY-1 has a high expression, Fas is low, something similar being observed in controls (P<.0003).*

Discussion

It is known that apoptosis takes part by diverse physiopathologic mechanisms in autoimmune diseases[13-16] and that Fas participates in the production of damage to glomeruli in SLE, because of its intense expression in the lupus nephropathy.[4,17-21] On the other hand, it has been described that YY-1 regulates the transcription of diverse genes by means of 3 different routes, repressing, activating, and initiating transcription.[22,23] There are studies that show the participation of YY-1 in the regulation of genes in tumor-like cell lines treated with nitric oxide, some genes of HIV, and certain alleles of chromosomes related to SLE.[12,24-27] Recent studies show that YY-1 regulates the loss of the expression of Fas in a model of ovarian and prostate cancer.[26] Nevertheless, no publications exist on the participation of YY-1 in the physiopathology of lupus nephritis and if this transcription factor regulates the loss of expression of Fas, a central protein in glomerular damage. The population studied with childhood lupus (18 patients) agrees with published data, type IV nephritis, predominance in women, an average age of 13 years and not affecting children of less than 5 years. The diagnosis of SLE was corroborated by the presence of antinuclear antibodies and double-stranded anti-DNA in all patients. Fifty-five percent presented, in addition, complement consumption. The group of low to moderate expression YY-1 displayed an unfavorable clinical course, with a greater percentage of macrocospic hematuria (27.7% of the patients), nephrotic syndrome (45%), lower creatinine clearance (91%), greater consumption of complement, and hyperazoemia (63.6%). Of these, 2 patients presented uremic syndrome that required dialysis and a third patient ended as chronic renal insufficiency. In contrast, the group of high YY-1 displayed a minor frequency of these alterations (no macrocospic hematuria or nephrotic syndrome, average creatinine clearance in 57%, and had hyperazoemia in 14%), and no one of this group had acute renal insufficiency. Although it is known that Fas is expressed mainly in the convoluted tubules, we found as much expression of Fas and YY-1 in tubules as in the glomeruli, mainly in lesions with a greater degree of cell proliferation, with a smaller density of expression for YY-1 and greater density of expression for Fas in these sites. Attention must be directed to the cellular distribution of YY-1 and Fas in the tubular level and mainly in the distal convoluted tubules apical membrane, important data for renal injury, because we know that there is great activity of ATPase dependent pumps on which some hormonal factors like aldosterone and vasopressin act, as well as regulation of Na and K, which are altered in the inflammatory process. The mitochondrial activity of this region indicates a greater amount of caspases. In the proximal convoluted tubules, where staining was also seen in variable degrees of intensity, there was a greater percentage of positive Fas cells in the lesions with greater cellular proliferation. It is in this site where greater reabsorption of the glomerular filtrate corresponds to solutos, and this damage goes hand in hand with a lower creatinine clearance, acute renal damage and hyperazoemia. The densitometry analysis sample shows YY-1 expression is inverse to the expression of Fas. Is interesting that, when YY-1 was found with an elevated density, the

expression of Fas was lower, which correlated with less clinical complications, a more favorable course of the disease, as well as less alterations in the renal function. It is interesting to point out that the high expression of YY-1 was similar in patients who had a favorable clinical course and in healthy controls. This fact indicates that YY-1 is important in the control of kidney homeostasis, something which had not been published to date. These findings indicate that YY-1 regulates to the loss of Fas expression in this type of injuries and agrees with reports in which this regulation takes place in some neoplastic cells. The results indicate that YY-1 participates in the physiopathology of lupus nephritis, a fact that had not been explored previously. This work requires more extensive study of YY-1 to evaluate its utility as a prognostic factor in this disease.

References

1. Cassidy JT, Petty RE. Textbook of pediatric rheumatology. 5th ed. Philadelphia: WB Saunders; 2005.
2. Yang LY, Chen WP, Lin CY. Lupus nephritis in children. A review of 167 patients. Pediatrics. 1994;94:335-40.
3. Orozco Alcalá J. Reumatología en niños. 1st ed. Barcelona: Masson; 2003. p. 69-80.
4. Ortiz A. Apoptotic regulatory proteins in renal injury. Nephrology forum. Kidney Int. 2000;58:467-85.
5. Takemura T, Murakami K, Miyazato H, Yagi K, Yoshioka K. Expression of Fas antigen and Bcl-2 in human glomerulonephritis. Kidney Int. 1995;48:1886-92.
6. Savill J. Regulation of glomerular cell number by apoptosis [revisión]. Kidney Int. 1999;56:1216-22.
7. Stollar BD, Stephenson F. Apoptosis and nucleosomes. Lupus. 2002;11:787-9.
8. Makino H, Sugiyama H, Yamasaki Y, Maeshima Y, Wada J, Kashiara N. Glomerular cell apoptosis in human lupus nephritis. Virchows Arch. 2003;443:67-77.
9. Wen FS, Xiurong Z, GUO M, Shanyan L. Dysregulation of apoptosis: a possible mechanism leading to chronic progressive renal histological changes in Lupus Nephritis. Chin Med J. 2000;113:1082-6.
10. Kirim S. Tammer T, Saime P, Gonlusen G. Apoptosis and proliferating cell nuclear antigen in lupus nephritis (class IV) and membranoproliferative glomerulonephritis. Ren Fail. 2005, 27(1):107-113.
11. Shy Y, Lee JS, Galvain KM. Everything you have ever wanted to know about Yin Yang 1 [revisión]. Biochim Biophys Acta. 1997;1332:F49-66.
12. Garban HJ, Bonavida B. Nitric oxide inhibits the transcription repressor Yin-Yang 1 binding activity at the silencer region of the Fas promoter: A pivotal role for nitric oxide in the up-regulation of Fas gene expression in human tumor cells. J Immunol. 2001;167:75-81.
13. Andersen MH, Reker S, Kvistborg P, Becker JC, Straten PT. Spontaneous immunity against Bcl-xL in cancer patients. J Immunol. 2005;175:2709-14.
14. Broker LE, Kruyt FA, Giaccone G. Cell death independent of caspases: a review. Clin Cancer Res. 2005;11:3155-62.
15. Yang E, Korsmeyer SJ. Molecular thanatopsis: a discourse on the BCL2 family and cell death. Blood. 1996;88:386-401.
16. Yang A, Walker N, Bronson R, Kaghad M, Oosterwegel M, Bonnin J, et al. p73-deficient mice have neurological, pheromonal and inflammatory defects but lack spontaneous tumours. Nature. 2000;404:99-103.
17. Sugiyama H, Kashihara N, Makino H, Yamasaki Y, Ota Z. Apoptosis in glomerular sclerosis. Kidney Int. 1996;49:103-11.
18. Papo T, Parizot C, Ortova M, Piette J-C, Frances C, Debre P, et al. Apoptosis and expression of soluble Fas mRNA in systemic lupus erythematosus. Lupus. 1998;7:455-61.
19. Badillo-Almaraz I, Daza L, Avalos-Diaz E, Herrera-Esparza R. Glomerular expression of Fas ligand and Bax mRNA in lupus nephritis. Autoinmunity. 2001:34:238-9.
20. Lorz C, Ortiz A, Justo P, González-Cuadrado S, Duque N, Gómez-Guerrero C, et al. Proapoptotic Fas ligand is expresed by normal kidney tubular epithelium and injured glomeruli. J Am Soc Nephrol. 2000;11:1266-77.
21. Tsukinoki T, Sugiyama H, Sunami R, Kobayashi M, Onoda T, Maeshima Y, et al. Mesangial cell Fas ligand: Upregulation in human lupus nephritis and NF-kappaB-mediated expression in cultured human mesangial cells. Clin Exp Neprhol. 2004;8:196-205.
22. Seto SYE, Chang LS, Shenk T. Transcriptional repression by YY1, a human GLI-Kruppel-related protein, and relief of repression by adenovirus E1A protein. Cell. 1991;67:377.
23. Flanagan JR, Becker KG, Ennist DL, Gleason SL, Driggers PH, Levi BZ, et al. Cloning of a negative transcription factor that binds to the upstream conserved region of Moloney murine leukemia virus. Moll Cell Biol. 1992;12:38.
24. Shrivastava A, Calame K. An analysis of genes regulated by the multifunctional transcriptional regulator yin yang-1. Nucleic Acid Res. 1994;22:5151.
25. Thomas MJ, Seto E. Unlocking the mechanisms of transcription factor YY-1: are chromatin modifying enzymes the key? Gene. 1999;236:197.
26. Jazirehi AR, Huerta-Yepez S, Cheng G, Bonavida B. Nitric oxide sensitizes prostate carcinoma cell lines to TRAIL-mediated apoptosis via inactivation of NF-kappa B and inhibition of Bcl-xl expression. Oncogene. 2004;23:4993-5003.
27. Tsao BP, Cantor RM, Grossman JM, Shen N, Teophilov NT, Wallace DT, et al. PARP alleles within the linked chromosomal region are associated with systemic lupus erythematosus. J Clin Invest. 1999;103:1135-40.