Journal of Clinical Immunology and Research

Research Article

A SCITECHNOL JOURNAL

Interferon-Inducible Gene (Lymphocyte Antigen 6 Complex Locus E) As a Biomarker of Disease Activity in Systemic Lupus Erythematosis Patients

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Abstract

Aim of the work: To assess the expression of type I interferon (IFN) inducible gene (Lymphocyte antigen 6 complex Locus E) in patients with SLE and to correlate expression Level with disease affair and/or severity.

Patients and methods: Peripheral blood samples have been collected from 40 patients with SLE patients and 25 healthy donors as a control. Total RNA was extracted and reverse transcribed into complementary DNA for all samples. Level of expression of interferon-inducible gene LY6E was measured by real time polymerase chain reaction (PCR), after which gene expression comparisons were performed between SLE patients and control subjects. Disease status was assessed according to the systemic lupus erythematosis disease activity index (SLEDAI) and systemic lupus international collaborating clinics/American college of rheumatology damage index (SDI).

Results: Type I Interferon-inducible genes (IFIGs) lymphocyte antigen 6 complex locus E (LY6E) was highly expressed in SLE patients compared with normal controls. Type I IFIGs (LY6E) was positively correlated with the SLEDAI scoring degree. Elevated Type I IFIGs (LY6E) was also correlated with the presence of cumulative organ damage (Systemic Lupus International Collaborating Clinics/American Society of Rheumatology Damage Index).Type I IFIGs (LY6E) was positively correlated with anti-double stranded DNA (anti-dsDNA) antibodies and negatively correlated with C3. LY6E level were positively correlated with proteinuria degree.

Conclusion: Type I IFIGs (LY6E) was highly expressed in SLE patients, the higher expression of LY6E gene in patients with SLE is closely associated with disease activity, degree of organ damage, proteinuria, and with anti-dsDNA antibody positivity titer and hypo-complementenemia. The LY6E may be a prospective biomarker to judge lupus activity clinically.

Keywords

Systemic lupus erythematosis; Disease activity; Type-1 interferone inducible gene; Lymphocyte antigen 6 complex locus E; LY6E gene

Introduction

Systemic lupus erythematosis (SLE) is a chronic autoimmune disease. The immune dysregulation resulting in the production of autoantibodies, of these; antinuclear antibody, circulating immune complexes, and activation of the complement system [1].

The characteristic heterogeneous course of SLE, results in affection of different individuals with a wide range of different manifestations. With unpredictable flares and improvements may be observed. There is no specific single diagnostic test for SLE, and therapy is typically initiated after signs of organ damage appear. There is an increasing interest in the identification of biomarkers for SLE, and to monitor disease activity that well allows earlier and more appropriate treatment. Also to provide insight into the relationships between pathogenesis and clinical manifestations [1-3].

Many authors were found a strong evidence of cytokines role in the pathogenesis of SLE. The first of these cytokines documented was an increased serum level of interferon (IFN) (subsequently characterized as IFNa), which is produced mainly by leukocytes [4-6]. There was a strong evidence of positive correlation between serum level of IFN-a in SLE and both disease activity and disease severity [4,7]. Also, it has been found that there was a strong relationship between IFN-a level and other markers of immune dysregulation activities, such as complement activation and double stranded DNA (dsDNA) antibody titers [4].

Type 1 interferon-inducible genes (IFIGs); a recently identified and studied interferon-a gene, has been found to be significantly upregulated in peripheral blood cells from SLE patients [8-11]. The expression of these IFIGs in SLE patients was found to be closely associated with increases disease activity. Also, IFIGs; often referred to as IFN signatures, was later found to be closely associated with specific autoantibody that signifies organ damage [12].

It has been reported that, about 20 type I IFN–inducible genes in peripheral blood cells from SLE patients [13]. Some studies [14-23] found that 5 genes explained 98% of the total variation for these genes. These 5 genes [Myxovirus resistance 1 (Mx1), Oligoadenylate synthetase (OAS)1, and Lymphocyte antigen 6 complex, locus E (Ly6e), Oligoadenylate synthetase–like (OASL), and Interferon-inducible protein (clone IFI-15K) (ISG15) were subsequently studied for differential expression between SLE patients and controls, and studied further to correlate their expression levels with disease activity and clinical features.

Lymphocyte antigen 6 complex locus E (Ly6E) (also known as thymic shared antigen 1 [TSA-1]), is a member of the Ly6 super family [14], it is a small glycosyl phosphatidylinositol linked surface protein expressed on hematopoietic stem cells, lymphocyte subsets (T, B and natural killer), and non-lymphoid tissues including liver and kidney cells [15].

Materials and Methods

Study participants

Two groups of study participants were enrolled. The systemic lupus erythematosis (SLE) group consisted of 40 patients with SLE

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Received: March 12, 2019 **Accepted:** May 13, 2019 **Published:** May 17, 2019

who fulfilled the revised American college of rheumatology (ACR) criteria for the classification of SLE [16] has been selected from rheumatology and rehabilitation department, Assiut university hospital, for the study.

25 healthy volunteers, sex and age matched with studied group, has been enrolled in the study serving as a control group, For each SLE patient, disease activity is mainly assessed by SLEDAI clinically at present, together with the help of inflammatory indicators as ESR, hypocomplement, titre of Anti-dsDNA and impaired organ status. SLEDAI consists of 24 items, of which 16 are clinical and eight are based solely on laboratory results [17]. A manifestation is recorded if it has been present at any point during the past 10 days, regardless of severity or whether it has improved or worsened. Weighting is used, resulting in individual item scores ranging from one to eight and a global score ranging from 0 to 105.

Disease status was assessed according to the systemic lupus erythematosis disease activity index (SLEDAI) and systemic lupus international collaborating clinics/American college of rheumatology damage index (SDI).Patients excluded from the study were those younger than 18 years and Patients with definite diagnosis for any other systemic autoimmune disorders. Informed consent was obtained from all patients. The study protocol was approved by ethical committee of faculty of medicine, Assiut University.

Data collection

Demographic and clinical data for patients and controls were obtained through complete medical history, physical and articular examinations including thorough clinical examination.

Disease activity/Cumulative damage evaluation

Disease activity was measured by the systemic lupus erythematosis disease activity index (SLEDAI) [18]. This index of activity (SLEDAI) includes 24 weighted items grouped into 9 domains, or organ systems, and each domain or organ affected will indexed and the score collected as follows: central nervous system (assigned a weight of 8), vascular system (weight of 8), renal system (weight of 4), musculoskeletal system (weight of 4), serosal system (weight of 2), dermal system (weight of 2), immune system (weight of 2), constitutional (weight of 1), and hematologic system (weight of 1). So, the SLEDAI scores will ranges from 0 to 105. Disease activity has been considered if the score ≥ 8 [19].

Also another scoring system, ranges from 0 to 27, for cumulative SLE-related damage in all patients has been assessed using the systemic lupus international collaborating clinics damage index (SLICC/ACR/DI) [20,21]. All these data will be recorded for every patient in a separate sheet.

Laboratory assessments

Complete blood picture (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibodies (ANAs), anti-dsDNA antibodies and serum complements C3 and C4 levels were done to all patients.

Urine sample collection twenty four hour protein collection of the urine sample, without preservative, for estimation of 24 hs urinary proteins.Urine protein concentrations were measured by the Bradford method [21].

Total RNA extraction and cDNA synthesis

Five mL of heparinised peripheral blood was taken from every study subject, and PBMCs were isolated by erythrocyte lysis method. Total RNA was extracted from the PBMCs using the Trizol reagent (GIBCO/BRL, Carlsbad, California, USA) according to manufacturer's instructions. The RNA purity was confirmed by the relative absorbance at 260/280 nm. Approximately 0.5 μg RNA of each sample was reverse transcribed to cDNA in a 22 μL volume using the superscript II RNase H– reverse transcriptase kit (Invitrogen, San Diego, California, USA). All RNA and cDNA samples were stored at -70°C.

Primers design and RT-PCR manipulation LY6E gene products are involved in regulation of lymphocyte activation.The primers were designed and synthesised by Takara Corp. (Dalian, China). The RT-PCR was taken on ABI Prism 7900HT Sequence Detector system (Applied Biosystems, Foster City, California, USA) by using SYBR Green I Dye (Qiagen GmbH, Valencia, California, USA). cDNA generated from a human T lymphocyte leukaemia cell line (Jurkat) was used as the calibrator sample.

The PCR amplifications were performed in a 5 μL volume at 50°C for two minutes and 95°C for 15 minutes, followed by 40 cycles of 95°C for 15 seconds, 55°C for 30 seconds and 72°C for 15 seconds. Fluorescence signals were collected at the annealing (55°C) and extension (72°C) phases. Each sample was run in triplicate wells.The results were analysed with sequence detection software version 2.1 (Applied Biosystems), and mRNA expression levels were calculated as ct value (relative quantification).

Radiological assessments

Conventional radiography:

- Chest x ray
- Hand x ray
- Feet x ray
- Abdominal ultrasonography.

Electrocardiography (ECG) and Echocardiography (Echo) for possible heart affection.Pulmonary function tests.

Statistical analyses

The data were coded and entered using the statistical package for the social science program (SPSS) version 17 Chicago. USA. The data were summarized using descriptive statistics: mean ± standard deviation (± SD), or frequencies (n) and percentages (%). Statistical differences between groups were tested using unpaired sample t-test. We use T. test to determine significance for numeric variables and we use Chi.square to determine significance for non-parametric variables. We use person's correlation for numeric variables in the same group.

P>0.05 non-significant

P<0.05 significant

P<0.01 moderate significant

P<0.001 highly significant

Results

The selected groups of study with the demographic characteristics of patient and control group with the clinical data and scoring index

for each group has been expressed as mean ± SD (Table 1).Level of expression of type I interferon-inducible gene, lymphocyte antigen 6 complex locus E in the SLE group (5.23 ± 2.17) was significantly higher than that in the control group (2.98 ± 0.74), P<0.001 (Table 2, Figures 1 and 2). It has been noticed that LY6E gene expression was increased with lupus activity, and according to its level patients were divided into high LY6E expression group (over value 6.745, n=18) and low LY6E expression group (between values 6.745 and 4.298, n=12), and the clinical data comparison including medication between these 2 groups were shown in Table 2.

It has been found that high LY6E expression group had higher SLEDAI score (20.75 ± 9.31) than low LY6E expression group (13.78 ± 6.75), P<0.02). And LY6E expression levels were strongly correlated with SLEDAI (r=0.396, P<0.01). As regards, the mean value of SLICC/ACR damage index in low LY6E was 2.28 and in high Ly6E was 4.25 with significant difference of SLICC/ACR damage index between low and high LY6E expression groups (P<0.05), which means that the high Ly6E expression is associated with increased SLICC/ACR damage index.

24 hrs urine proteins is an effective indicator reflecting renal damage and represent active nephritis. Our study showed that high LY6E expression group had higher 24 hrs urine protein (2848.17 ± 1599.84) than low LY6E expression group (1179.89 ± 338.73, P=0.02) (Figure 3).

Table 1: Demographic characteristics of SLE patients and healthy controls.

Total number	40	25
Age, years (range)	26.9 ± 7.90 (18.0-48.0)	35.3 (21–54)
Female/male (female %)	39/1 (97.5)	23/2 (95)
Duration, years (range)	3.16 ± 2.54 (0.0-12.0)	NA
SLEDAI (range)	13.17 ± 6.82	NA
SLICC/ACR damage index	3.18 ± 2.26	NA
LY6E expression (range)	5.33 ± 2.1	4.52 ± 1.63(1.14-8.75)
Glucocorticoids use (%)	34 (85.0%)	NA
Mean dose (mg/day)	10–30 mg/day	
Immunosuppressive agent use, cases (%)	AZA 30 (75.0%), CYC 27 (67.5%), MTX 5 (12.5%), HCQ 30 (75.0%)	NA

Table 2: Comparison of SLE patients with high or low LY6E expression

Item	**Low Ly6E"<4.2" n=18**	**High Ly6E">6.7" n=12**	**P= value**
Age	27.50±7.59	27.33±9.24	P=0.957 n.s
Disease duration(years)	3.33±3.02	3.04±2.47	P= 0.783 n.s
Malar rash :			
- ve	11 (61.1%)	9 (75%)	P=0.685 n.s
+ ve	7 (38.9%)	3 (25%)	
Photosensitivity :			
- ve	6 (33.3%)	6 (50%)	P=0.556 n.s
+ ve	12 (66.7%)	6 (50%)	
Oral ulcers :			
- ve	13 (72.2%)	6 (50%)	P=0.460 n.s
+ ve	5 (27.8%)	6 (50%)	
Alopecia :			
- ve	12 (66.7%)	6 (50%)	P=0.659 n.s
+ ve	6 (33.3%)	6 (50%)	
Arthralgia :			
- ve	15 (83.3%)	8 (66.7%)	P=0.174 n.s
+ ve	3 (16.7%)	4 (33.3%)	
Serositis :			
- ve	16 (88.9%)	9 (75%)	P=0.208 n.s
+ ve	2 (11.1%)	3 (25%)	
ESR mm/h	62.38±25.50	78.33±27.87	P=0.117 n.s
24 h urine protein (normal < 0.3 g)	1179.89±338.73	2848.17±1599.84	P= 0.0230*
C3	116.00±39.67	102.50±38.82	P<0.03*
Anti-dsDNA titre	3.65±2.64	6.41±2.71	P<0.01*
ANA titre	0.94±0.53	1.17±0.83	P=0.382 n.s
SLEDAI score	13.78±6.75	20.75±9.31	P<0.02**
SLICC/ACR damage index	2.28±1.52	4.25±2.52	P<0.01*

Lower complement C3 level in blood is a predictive of more formation and consumption of immune complexes, suggesting severe autoimmune response in body. Our results reveals a remarkably lower C3 level in high LY6E expression group (102.50 ± 38.82) than in low LY6E expression group (116.00 ± 39.67, P<0.03). C3 levels were negatively correlated with LY6E expression (r=-140, P<0.03) (Figures 4 and 5) There was an increase in anti-dsDNA titre in patients with high LY6E expression group (6.41 ± 2.71) than with low LY6E expression group (3.65 ± 2.64, P<0.01). Circulating levels of IgG anti-dsDNA showed a positive correlation with LY6E expression (r=0.307, P=0.054).

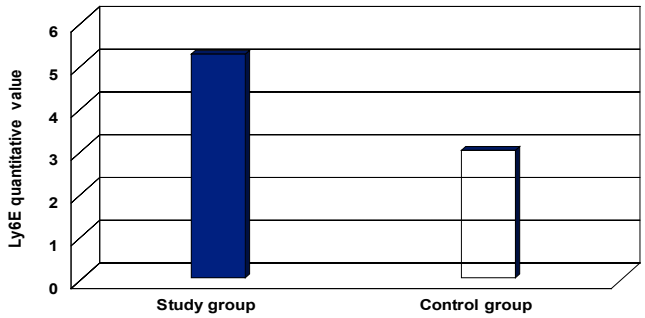

Figure 1: Relation of LY6E quantitative value in both study and control groups.

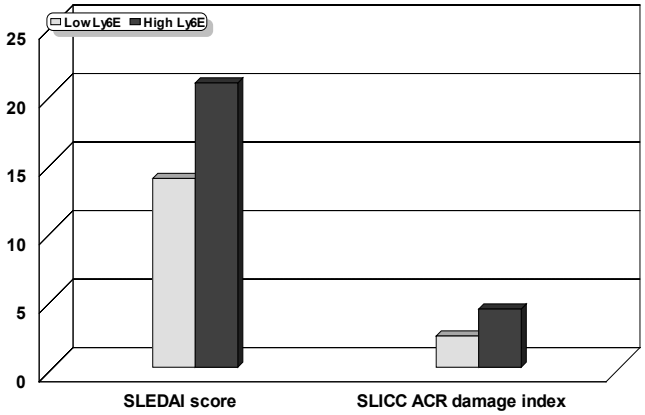

Figure 2: SLEDAI score and SLICC/ACR damage index in low Ly6E <4.29 and High Ly6E >6.7.

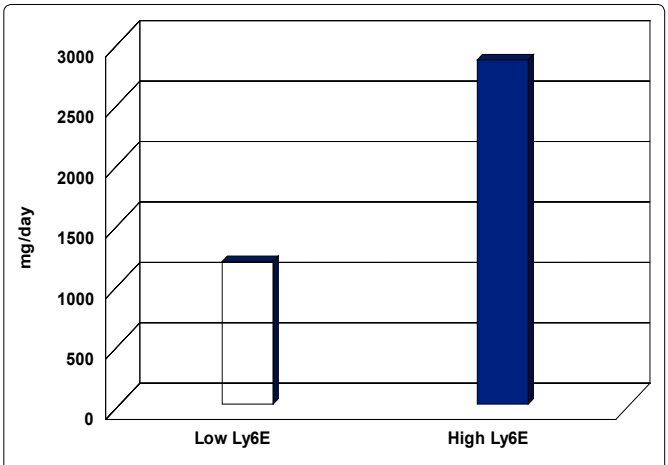

Figure 3: Urine 24 h protein in Low and high Ly6E.

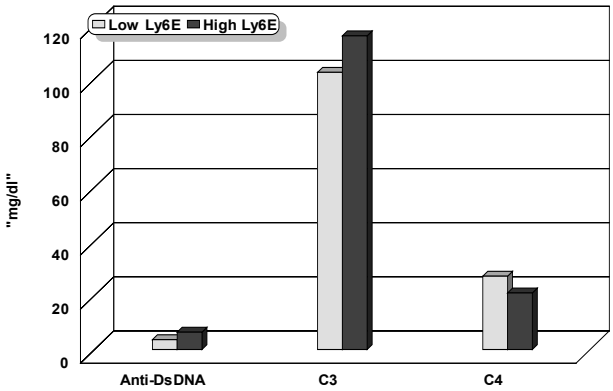

Figure 4: Anti-Ds DNA, C3 and C4 in low Ly6E <4.29 and High Ly6E >6.

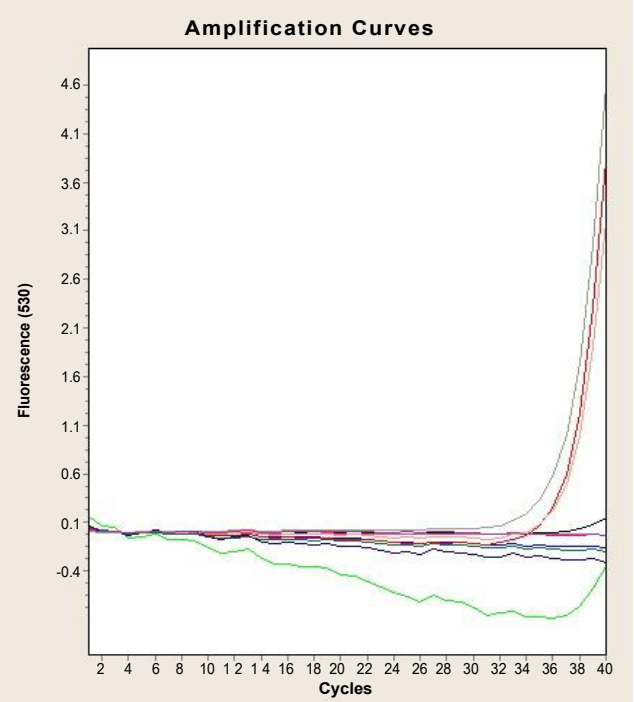

Figure 5: Ligand mRNA expression levels were calculated as negative delta- delta ct value (relative quantification). Ly6E gene is expressed in 3 patients by real time PCR.

Subjects were considered to have active renal disease if proteinuria was 0.5 gm/day, hematuria was 5 red blood cells per high-power field (hpf), pyuria was 5 white blood cells/hpf, or cellular casts were present. Infection, kidney stones, or other causes were excluded.

LY6E expression levels were significantly higher in patients with active renal disease than in those patients with inactive lupus nephritis at the time of blood drawing (P=0.02).

From our data we found that, there was no correlation between LY6E gene expression and lupus clinical manifestations as malar rash, photosensitivity, alopecia, oral ulcers and arthralgia serositis; or with laboratory findings, such as ESR, leukopenia, thrombocytopenia and ANA titre (Table 2).

Discussion

Systemic lupus erythematosus (SLE) disease is characteristic by heterogeneous course, with affection of different individuals with a wide range of different manifestations. It is a complex autoimmune disease with the presence of antibodies to nuclear components [22,23]. The characteristic immunologic abnormalities in SLE affected by genetic, epigenetic, environmental and hormonal factors which interact to contribute to and leads to disease pathogenesis [24].

Immunostimulatory nucleic acid autoantigens including dsDNA may act as endogenous adjuvants by promoting IFN-I production and dendritic cell maturation [25].

Lymphocyte antigen 6 complex locus E (Ly6E) (also known as thymic shared antigen 1 [TSA-1]), a member of the Ly6 superfamily [14], is a small glycosyl phosphatidylinositol linked surface protein expressed on hematopoietic stem cells, lymphocyte subsets (T, B, and natural killer), and nonlymphoid tissues including liver and kidney cells [15].

Regarding the initialling factors in IFN pathway, there have been a lot of studies showing that the type I IFN contributes to the pathogenesis of lupus [26,27] Our results indicated that type I IFIGs (LY6E) in patients with SLE are higher than in non-SLE patients.

Proteins of IFIGs (interferon induceble genes) can be autoantigens to trigger autoimmune response in mice [28]. In mice models, in-vivo delivery of murine IFN α leads to a rapid and severe disease with characteristics of lupus [12], and knockout of IFN type I receptors prevents from occurrence of disease [29].

In consistent with the results of many studies [1,23,27], our study demonstrated that patients with SLE with high expression of LY6E gene had more active disease and higher SLEDAI score than patients with low LY6E gene expression ($P<0.01$).

The function of Ly6E in the immune system is believed to participate in cell signalling and cell adhesion processes [30,31]. Recently, it is reported that surface expression levels of Ly6E on peripheral lymphocytes positively correlate with disease severity in several lupus prone strains of mice [32,33].

Nakajima et al. [32] suggesting a potential role of LY6E in the pathophysiology of renal disease. They found that Ly6E is highly expressed in renal proximal tubules in response to proteinuria, identified by gene expression profiles and confirmed by laser microdissection along with real time PCR. These findings are consistent with our findings of markedly elevated LY6E gene expression in patients with SLE with high proteinuria and lower blood complement.

Lupus nephritis is a severe complication in patients with SLE, and proteinuria monitoring is an effective approach in guiding clinical treatment for renal lesion. This study found that patients with SLE with higher expression of LY6E gene had a high 24 hrs urine protein than patients with low LY6E gene expression ($P<0.05$) i.e the higher the level of proteinurea the more gene expresion.

Many studies [1,23,27,41] found that there was a positive correlation between proteinurea level and Ly6E gene expresion in lupus nephritis. Furthermore, patients with SLE with higher expression of LY6E gene had lower blood complement C3 than patients with low LY6E expression ($P<0.03$). These results are in consistant with our findings of hypo-complementanaemia (decrease Complement-3) in lupus nephritis patients especially with highly expressed Ly6E gene.

In agrrement with many studies [8,34] we were found that, presence of proteinurea and lupus nephritis and anti-dsDNA antibody titre are associated with increased expression of IFN-inducible genes (IFIGs) in peripheral blood mononuclear cells (PBMCs).

The significant negative association between complement levels and IFIG expressions may reflect the role of immune complexes in both complement activation and IFN production [35-37].

Concerning other clinical manifestations, our data did not found any significant association of LY6E gene expression with lupus clinical manifestations as malar rash, photosensitivity, alopecia and oral ulcers or with laboratory findings as ESR, anti-dsDNA titre, which was in contrast to the results of some studies [38-40]. However, our results regarding the clinical manifestations are in consistant with the results of many other researchers [1,23,27,40].

IFIG expression level can be used to classify SLE patients into subgroups with different severity characterized by renal disease, complement activation, and autoantibody production to RNA-associated autoantigens [38,39].In the present study we found that IFIG expression LY6E was associated with disease activity, as assessed by using the SLEDAI score and C3 level.

Also, our study shows a highly expressed LY6E gene in patients with ongoing or cumulative organ damage, as assessed based on the presence of active lupus nephritis (LN) or SDI score in SLE patients.

Conclusion

Combining these findings with the above mentioned, we conclude that LY6E should be a prospective biomarker in judging lupus activity clinically. High expression of LY6E may thus be helpful to identify SLE patient with active and severe disease.

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