Exploring the role of long non-coding RNA GAS5 in Systemic Lupus Erythematosus patients

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Abstract

Background: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease of heterogenous pathogenesis; environmental, immunologic, genetic, and epigenetic. Long noncoding RNA (lncRNAs) are recently considered emerging biomarkers for diagnosis of SLE. Intense research has been conducted to unveil the association of different lncRNAs and clinical characteristics of SLE as well as disease activity. **Objectives:** We aim to evaluate the expression level of lncRNA GAS5 in serum of SLE patients in comparison with healthy controls and assess its correlation with Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and Systemic Lupus International Collaborating Clinics/ American College of Rheumatology (SLICC/ACR) Damage Index (SDI). **Methods:** 30 adult patients with SLE as well as 20 apparently healthy controls. All patients were subjected to full history taking, thorough clinical examination and laboratory investigations in the form of CBC, kidney and liver function tests, acute phase reactants (hsCRP, ESR) and immunological profile (C3, C4, anti-dsDNA antibodies). SLE disease activity was assessed by SLEDAI-2K and SLE damage was assessed by SDI. The expression levels of GAS5 were measured by quantitative real time PCR. **Results:** LncRNA GAS5 expression levels were insignificantly upregulated in SLE patients compared to control group (p value > 0.05). Their expression levels were not associated with any of clinical or laboratory characteristics of lupus patients except for patients with ocular involvement in whom they were unexpectedly found to be significantly lower (p value 0.03). Also, GAS5 was not associated with SLEDAI-2K or SDI scores. **Conclusion:** LncRNA GAS5 may be considered a diagnostic biomarker for SLE diagnosis, but not a reliable biomarker for assessment of SLE activity or damage.

Keywords: GAS5, long non-coding RNA, Systemic lupus erythematosus, SLE activity index (SLEDAI-2K), SLE damage index (SDI)

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect almost any organ system, although it mainly involves the skin, joints, kidneys, blood cells, and nervous system **(1)**. It is a multisystem affection with recurrent episodes of exacerbation and remission with higher incidence rate in women of childbearing age **(2)**. The pathogenesis of SLE is still incompletely elucidated.

The study of epigenetic phenomena in SLE provides new insights into the disease pathogenesis and suggests possible potential biomarkers of disease activity. Long non-coding RNAs (lncRNAs) are transcripts with more than 200 nucleotides but no ability to code for proteins. They are emerging as an important regulator of gene expression via epigenetic modification, transcriptional and post transcriptional regulation **(3)**. In the context of cancer, lncRNAs have been the subject of substantial research due to their potential role in gene regulation and disease pathogenesis **(4)**. Inflammation **(5)** and innate and adaptive immunity are also involved **(6)**. Diverse lncRNAs were discovered to have altered expression levels in SLE. The potential of these lncRNAs as biomarker for diagnosis, therapy, and prognosis was demonstrated by their correlation with clinical presentation and disease activity **(7)**. lncRNAs research in SLE is a nascent and developing field. The exact role of these lncRNAs and how they integrate in SLE pathogensesis is still unknown and needs more research.

The lncRNA Growth-arrest specific transcript 5 (GAS5) is a 5 □terminal oligopyrimidine class of genes which control cell growth, proliferation and apoptosis **(8)**. There is genetic evidence that GAS5 is located within chromosome region 1q25, which is an SLE-susceptible locus. This indicates a likely link between GAS5 and SLE susceptibility. It has been linked to an increased risk of developing SLE in mice models **(9)**. Recently published studies investigated GAS5's function and correlation with SLE disease activity **(10-12)**. With an AUC > 0.80 and a high sensitivity and specificity, as shown by

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ROC analysis, GAS5 can differentiate SLE patients from healthy controls (13). Based on these studies, GAS5 is considered a recently discovered biomarker in SLE. However, it is still unknown how it is incorporated in the autoimmune process and the continuous drive of inflammation and tissue damage. Studies on GAS5 in atherosclerosis and intervertebral disc degeneration showed that overexpression of GAS5 levels significantly increase apoptosis and increase expression of apoptotic factors such as caspases, while their knocking down decrease apoptosis (14, 15). Other than expected, SLE patients showed a significant reduction in GAS5 expression compared to the healthy controls (10, 11, 13). However, Suo Q et al., suggested upregulation of the expression levels of GAS5 in SLE (12).

In our study we aim to investigate the role of GAS5 in SLE patients and correlate their expression levels with disease activity and damage indices, thus using it as a novel non-invasive marker for diagnostic and prognostic purposes.

Methods

This study included 30 adult patients with diagnosis of SLE according to the 2012 Systemic lupus International Collaborating Clinic (SLICC criteria) (16), as well as 20 apparently healthy controls (age and sex matched). The patients were recruited from Internal Medicine Inpatient Department as well as Outpatient Rheumatology and Clinical Immunology clinic of Internal Medicine Department, at Kasr Alainy, Cairo University. Patients with malignancy, recent infection in the last 6 weeks or patients with other autoimmune diseases were excluded from the study.

After obtaining a written informed consent from the patients and after ethical committee approval, all subjects with eligibility criteria were subjected to thorough history taking and systemic clinical examination including fundus examination. Laboratory investigations include complete metabolic profile, acute phase reactants (ESR, hsCRP) and immunological profile (Anti-dsDNA antibodies (anti-ds DNA), C3 and C4). Renal biopsy was performed if urine protein excretion of 500 mg/day or greater, cellular casts, unexplained hematuria (RBCs more than 5 cells per high power field), unexplained pyuria (WBCs more than 5 cells per high power field) or unexplained increases in serum creatinine, and pathological assessment was done according to the International Society of Nephrology/ Renal Pathology Society 2003 classification system to determine the class of LN as well as the parameters of activity and chronicity (17).

Assessing the SLE activity damage indices was done by Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) (18) and The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) (19). Quantitative real-time PCR measurements of expression levels of GAS5 in plasma of SLE patients as well as the control group.

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 27.

Results

This study was conducted at Kasr El-Ainy hospitals, Cairo university. It was conducted on 50 subjects; 30 patients with SLE were diagnosed according to the 2012 Systemic lupus International Collaborating Clinic (SLICC criteria) and 20 apparently healthy individuals.

The Clinical and laboratory characteristics and dose of steroids in SLE group are illustrated in tables 1,2,3 and figure 1.

In our study, we found that there are increased expression levels of lncRNA GAS5 gene in cases as compared to control group with no statistically significant differences (p value 0.113). At cut-off value 1.3-fold change, GAS5 could discriminate SLE from control (AUC 0.63) with high specificity 100% and modest sensitivity 63%. LncRNA GAS5 expression levels were statistically significant lower in SLE patients with ocular involvement (p value 0.035). Ocular affection in SLE group included macular exudates, maculopathy, peripheral vascular sheathing, retinal artery occlusion, posterior subcapsular cataract, hypertensive changes, and sensorineural retinal detachment.

There was no statistically significant correlation of GAS5 gene expression levels with age in years, duration of illness in months or dose of steroids (prednisone equivalent) at time of recruitment or to cumulative dose of steroids in the last 6 months before recruitment. No statistically significant difference of expression levels of lncRNA GAS5 regarding mucocutaneous, musculoskeletal, pulmonary, cardiovascular, gastrointestinal, neuropsychiatric, hematological involvement and presence of lupus nephritis in SLE patients.

There was no statistically significant correlation between expression levels of GAS5 with hemoglobin, total leucocytic count, platelets, urea, creatinine, ESR, high sensitivity CRP, 24-hour urinary proteinuria, complement 3 and complement 4. There was no statistically significant difference of expression levels of GAS5 regarding presence of active urinary sediments or presence of consumed C3 or C4.

There was no statistically significant correlation between expression levels of lncRNA GAS5 with total SLEDAI-2K score and SDI.

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Table 1: Clinical characteristics of SLE patients

		n (%)
Clinical characteristics	Constitutional symptoms	11(37)
	Mucocutaneous manifestations	29(97)
	Musculoskeletal manifestations	13(43)
	Pulmonary involvement	6(20)
	Cardiovascular involvement	12(40)
	Gastrointestinal involvement	1(3)
	Neuropsychiatric involvement	3(10)
	Ocular involvement	18(60)
	Hematological Involvement	24(80)
	Antiphospholipid syndrome	8(27)
	Lupus Nephritis	21(70)
Total SLEDAI-2K Score	**Mean (SD)**	17.8 (12.2)
	Median (range)	17 (12,21)
SDI Score	**Mean (SD)**	1.7 (1.8)
	Median (range)	1 (0,2)

Table 2: Steroid dose in SLE patients

	Median	IQR (25%-75%)
Dose of steroids at time of recruitment (prednisone equivalent)	30 mg	(15-60)
Cumulative dose of steroids of the last 6 months (prednisone equivalent)	1522 mg	(550-4854)

Table 3: Laboratory characteristics of SLE patients

	Mean	SD	Median	IQR (25%-75%)	
HB (gm/dl)	10.3	1.9			
TLC (cell/mm3)	7.2	3.5			
PLT (per mm3)			214	105	267
Urea (mg/dl)			39.5	30	62
Creatinine (mg/dl)			1	0.7	1.6
24-hour urinary proteins (mg/Day)			790	178	2300
ESR (mm/hour)			60.5	33	110
HsCRP (mg/l)			22	8.7	41.3
Complement 3 (mg/dl)	77.2	36.4			
Complement 4 (mg/dl)			15.5	8.4	23
HsCRP = high sensitivity CRP					

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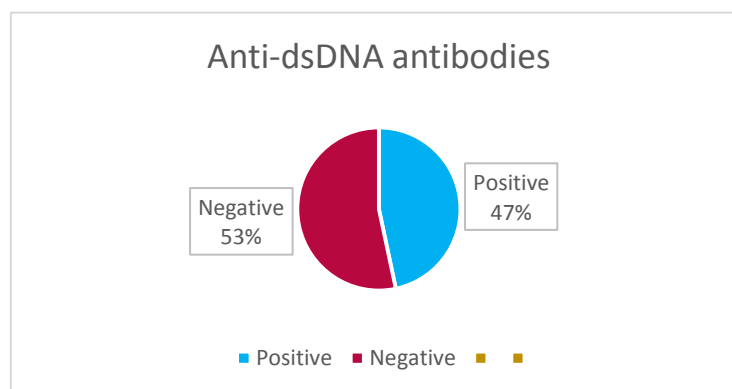Eur. Chem. Bull. 2023, 12(Issue 7), 2735-2740

Figure 1: Anti-dsDNA in cases

Discussion

SLE is a chronic autoimmune disorder that causes damage to multiple tissue/organs by generating autoantibodies and immune complexes. Genetics, immunology, environment, and hormones all play a role in the pathogenesis of SLE, albeit underlying mechanisms are uncertain **(20)**. Thus, understanding the pathways of development of SLE would help in the identification of novel therapies.

LncRNAs might add a new level of molecular control over SLE. Circulating lncRNAs in plasma or serum has been an emerging field for non-invasive diagnostic applications **(21)**. GAS5 was first found in growth arrest cells when the concept of lncRNA is emerging in 1988 to 1992 **(22)**. It was recognized earlier as a tumor suppressor of various kinds of cancers. However, evidence links it to SLE, rheumatoid arthritis, and Sjogren syndrome. It has been associated with increased risk for developing SLE in a mouse model **(9)**. In addition, GAS5 has been shown to be involved in development of human SLE **(23)**. LncRNA GAS5 was assumed to be incorporated in pathogenesis of SLE through different mechanisms. Bioinformatic analysis identified probable binding site between miR21 and GAS5 **(24)**. miR21 abnormality is a contributor to SLE development **(25)**. LncRNA-mRNA co-expression network analysis showed that GAS5 was involved in SLE pathogenesis through mitogen-activated protein kinase (MAPK) pathway **(11)**. MAPK signaling pathway can control immune response of T and B cells as well as the production of multiple SLE-related inflammatory cytokines, such as TNFα, IL-1/6 and IFN **(26)**. GAS5 also regulated Th17 differentiation and maintained the balance between Th17 and Treg cells **(27)**. Moreover, GAS5 upregulates caspase-3, caspase-7, and caspase-9 while inhibiting GR target genes involved in apoptosis control, such as cellular inhibitor of apoptosis 2 and serum GC-regulated kinase 1 **(12)**. Excessive apoptosis leads

to an increase in autoantigen-antibodies complexes, which is the endogenous trigger for IFN production and continuous circle of ongoing inflammation **(28)**.

In the present study we investigated serum expression levels of lncRNA GAS5 as a potential biomarker for diagnosing SLE patients. Our study showed elevated expression levels on lncRNA GAS5 in lupus patients compared to control group. However, with no significant statistical difference. Suo et al., demonstrated elevated lncRNA GAS5 expression levels in the CD4 T cells of SLE patients **(12)**. However, there was controversy regarding lncRNA GAS5 expression levels in SLE patients in the literature. Other studies depicted low level of lncRNA GAS5 in plasma **(10, 11, 13, 29, 30)**, CD4 T cells **(29, 30)**, B cells **(29)** and peripheral blood mononuclear cells (PBMC) **(24, 31, 32)** of SLE patients. This significant difference among studies reflects different populations, different genetic, epigenetic, and environmental backgrounds.

We found no significant association between expression levels of lncRNA GAS5 and any of the demographic, clinical characteristics of lupus patients such as gender, mucocutaneous, musculoskeletal and lupus nephritis or laboratory data such as ESR, C3, C4 and anti-dsDNA antibodies positivity. This comes in agreement with previous publications in this regard **(11, 24, 31)**. However, sporadic studies with relatively smaller sample size, found an association between the expression levels of lncRNA GAS5 and mucosal ulcers **(12, 13)**, rash **(13)**, consumed C3 **(12)**, ESR **(10)** and the presence of lupus nephritis **(32)**. The divergence of results could be due to the difference of sample size in each study. Our study demonstrated lower expression levels of lncRNA GAS5 in patients with ocular involvement compared to those without, while Jun Li et al., found no statistically significant association

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between GAS5 and visual affection in SLE (31). We found no explanation to this finding.

Consistent with the previously mentioned studies, we couldn't demonstrate a relation between expression levels of GAS5 and SLEDAI-2K total score. We also examined the correlation between the expression levels of lncRNA GAS5 and SDI score and we found it non-significant. Hence, lncRNA GAS5 could be a potential biomarker for diagnosis of SLE, but it is not a reliable prognostic biomarker of SLE activity or damage.

LncRNA GAS5 has been linked to glucocorticoid resistance for years **(33, 34)**. In the cytoplasm, glucocorticoid bind to and activate GR. The glucocorticoid receptor element (GRE) and activated cytosolic GR cooperate in the nucleus to promote the transcription of anti-inflammatory genes while inhibiting the transcription of proinflammatory genes. Therefore, interfering with GR's ability to bind to DNA can serve as a steroid action inhibitor **(35)**. GAS5 gene is a small nucleolar RNA host gene, containing C/D box small nucleolar RNA genes in its intron 16. The encoded transcript's secondary RNA structure mimics GRE in part, allowing it to attach to GR's DNA binding domain **(33)**. These results suggest this activity may regulate GC sensitivity and resistance by inhibiting GR activation and preventing GR from controlling gene transcription. This is in concordance with the observations from different experimental studies where lncRNA GAS5 was highly expressed in the PBMC from healthy individuals which exhibited poor response to invitro treatment with methylprednisolone for 72 hours as compared to cells that showed good response **(34)**. GAS5 was also unregulated in PBMC of severe asthmatic patients, who acquired higher doses of steroids as compared to non-severe asthmatic patients included in the study **(36)**. Additionally, GAS5 expression levels were found to be significantly increased in lung tissue of steroid insensitive murine models in comparison with the control group. Moreover, invitro treatment of cells with steroids (e.g., dexamethasone or methylprednisone) yielded in reduction of expression levels of GAS5 to variable extent, but GAS5 levels were still higher in steroid resistant cells as compared to steroid sensitive cells **(34, 36, 37)**. One can hypothesize that overexpression of GAS5 impedes GC activity, and thereby patients may require higher steroid doses during the course of their illness to overcome the effect of GAS5 on steroid actions.

In our study, we found that there is a positive correlation between the cumulative dose of steroids and the expression levels of GAS5 in SLE patients. However, it was not statistically significant. Further studies are needed to analyze the relation between lncRNA GAS5 expression levels and type, dose, and duration of steroids in SLE.

Conclusion:

We conclude that GAS5 may be considered a potential diagnostic biomarker in SLE. However, it is unreliable detector of SLE activity or damage. Further studies are recommended to be performed on a larger sample size and different genetic backgrounds to further describe lncRNA GAS5 expression levels in SLE patients.

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