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Original Article

Association of soluble TREM-like transcript-1 with clinical features and patient reported outcomes in systemic lupus erythematosus

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Abstract

Objective: The soluble triggering receptor expressed on myeloid cells (TREM-1)-like transcript 1 (sTLT-1) has a modulatory effect on the activation of TREM-1. We compared plasma sTLT-1 levels between patients with systemic lupus erythematosus (SLE) and healthy individuals and determined the association between sTLT-1 levels and clinical features and patient-reported outcomes (PROs) among patients with lupus.

Methods: An unmatched case-control study was conducted in 46 patients with SLE and 28 healthy subjects. sTLT-1 plasma levels were determined using enzyme-linked immunosorbent assay. Demographic factors, SLE manifestations, comorbidities, pharmacologic profile, disease activity (per SLAM-R), damage accrual, and PROs (as per Lupus Patient-Reported Outcome [LupusPRO]) were studied.

Results: Patients with SLE were found to have lower sTLT-1 levels compared with healthy individuals (9.0±7.2 vs. 18.6±22.3 pg/mL, p=0.008). Among patients with SLE, higher sTLT-1 levels were found in those taking corticosteroids (11.1±8.8 vs. 6.9±4.6 pg/mL, p=0.014). Significant correlations were found for the cognition (r=-0.442, p=0.027) and desires/goals (r=0.435, p=0.030) domains of LupusPRO. A tendency was observed between sTLT-1 levels and the SLAM-R (r=-0.278, p=0.064) and the lupus symptoms (r=-0.388, p=0.055) and physical health (r=-0.382, p=0.060) domains of LupusPRO.

Conclusion: Compared with healthy individuals, sTLT-1 levels were significantly lower in patients with SLE. Among patients with SLE, correlations were observed for some domains of LupusPRO. Given that sTLT-1 has anti-inflammatory properties, the deficiency of this protein could play an important role in the pathogenesis of SLE.

Keywords: Systemic lupus erythematosus, soluble TREM-like transcriptase 1, clinical manifestations, disease activity, disease damage, patient-reported outcomes

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, multi-systemic, autoimmune disease caused by the malfunctioning of the innate and adaptive immunities (1). Multiple etiologies such as genetic, epigenetic, and environmental factors seem to play a key role in the development of SLE. In this condition, the immune system loses self-tolerance and the ability to control excessive inflammation that results in organ damage. It has been proposed that the dysfunction of B-cells immunity, T-cell signaling, apoptotic cell clearance, cytokines, and complement cascade may contribute to its pathogenesis (2).

There is emerging evidence that cellular receptors such as Toll-like receptors (TLR) are involved in cellular signaling that activates the innate immunity upon recognition of a pathogen by macrophages, monocytes, dendritic cells, and neutrophils (3). Likewise, another family of receptors that works synergistically with TLR is the triggering receptors expressed on myeloid cells (TREM-1). These receptors are found on cellular membranes of macrophages, monocytes, and neutrophils (4). TREM-1 receptors were first recognized amplifiers of the inflammatory reaction triggered by sepsis (5) and then implicated in autoimmune inflammatory conditions such as rheumatoid arthritis (RA) (6) and inflammatory bowel disease (7). The role of the TREM-1 family and its soluble counterparts are being studied in the context of SLE, and they have been found to be elevated in patients with SLE (8). Also, compared with healthy individuals, the soluble part

of TREM-1 receptor (sTREM-1) was found to be higher in patients with SLE (9).

TREM-like transcript 1 (TLT-1) is a cellular receptor that functions as an inhibitor of the TREM cluster family (10). This receptor is specific to the α-granules of platelets and megakaryocytes. Upon platelet activation, it moves to the surface and its soluble part (sTLT-1) is released into plasma (11). High sTLT-1 serum levels have been found in patients with sepsis as well as with disseminated intravascular coagulation (11). Also, it has been shown that sTLT-1 modulates leukocyte activation by affecting TREM-1 stimulation and this molecule consequently functions as an inhibitor of the inflammation cascade to achieve homeostasis and prevent tissue damage (12).

The role of sTLT-1 in the pathogenesis of SLE has not yet been described. Hence, we sought to examine plasma sTLT-1 levels between patients with SLE and healthy individuals and determine the association between sTLT-1 levels and clinical manifestations, comorbidities, medications, disease activity, damage accrual, and patient reported outcomes (PROs) in patients with SLE.

Methods

Patient population

An unmatched case-control study was performed in 46 patients with SLE and 28 healthy individuals. Patients with SLE were recruited at the Clinical and Translational Research Consortium of Puerto Rico between March 2012 and June 2012. Both study groups comprised individuals aged ≥21 years and of Puerto Rican ethnicity. Patients with SLE fulfilled the American College of Rheumatology (ACR) revised classification criteria (13). Healthy subjects did not present any systemic or chronic disease. Control subjects included patients' friends or relatives accompanying patients with SLE to their scheduled medical visit or University of Puerto Rico Medical Sciences Campus (UPR-MSC) employees. Subjects who were unable to comprehend the informed consent form, pregnant women, and those with recent infections (within one month of the study visit) were excluded. The Institutional Review Board of the UPR-MSC Human Research Protection Office approved this study (protocol #7510112).

sTLT-1 levels

sTLT-1 plasma levels were measured as per the protocol described by Esponda et al. (14). Briefly, peripheral blood was collected into tubes containing 3.2% sodium citrate. Blood samples were maintained at room temperature and sent to the clinical laboratory within 30 minutes. Plasma was isolated by centrifugation at 1,500 rpm for 15 minutes. Supernatant was stored at -20°C. Afterward, sTLT-1 levels were measured using a commercial DuoSet ELISA Development kit (catalog number DY2394- R&D Systems, Inc. Minneapolis, Minnesota, USA).

Variables

At the study visit, the following variables were examined: demographic factors, cumulative SLE manifestations, comorbidities, pharmacologic profile, disease activity, damage accrual, and PROs. Clinical variables were available for each patient as part of an existing database. Demographic factors included age, sex, and SLE duration. Clinical domains included ACR criteria SLE manifestations (13) and Raynaud's phenomenon. Selected comorbidities included diabetes mellitus; arterial hypertension; arterial vascular events (myocardial infarction, angina pectoris and/or a vascular procedure for myocardial infarction, stroke, claudication and/or evidence of gangrene); venous thrombosis; and hypothyroidism. Among medications, treatments for lupus (corticosteroids, non-steroidal anti-inflammatory drugs [NSAIDs], hydroxychloroquine, mycophenolate mofetil, and azathioprine) and for selected comorbidities (angiotensin converting enzyme inhibitors [ACE inhibitors], angiotensin receptor blockers [ARB], statins, and aspirin [ASA]) were assessed. Disease activity was determined using the Systemic Lupus Activity Measure-Revised (SLAM-R) (15). Disease damage was ascertained using the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index (SDI) (16). PROs were measured using the Lupus Patient-Reported Outcome (LupusPRO) questionnaire (17). This instrument is self-administered and has been validated for assessing PROs in patients with SLE. It has eight health-related quality of life (HRQOL) domains and four non-HRQOL domains. HRQOL domains include lupus symptoms, cognition, lupus medications, procreation, physical health, pain/vitality, emotional health, and body image and non-HRQOL domains contain desires/goals, social support, coping, and satisfaction with medical care.

Statistical analysis

Continuous variables were evaluated using the measures of central tendency and dispersion. The Student's t-test was used for comparing sTLT-1 levels from patients with SLE and healthy/control subjects. Sub-analysis among patients with SLE was performed using unpaired Student's t-test (or Mann-Whitney U test in case of non-normal distribution) for comparing sTLT-1 levels with demographic, clinical, pharmacologic, disease activity, disease damage, and PRO variables. Lastly, for evaluating the association between sTLT-1 levels with SLAM-R and LupusPRO, correlation analysis was performed using the Pearson correlation coefficient (or Spearman's rank order correlation as appropriate). The statistical software STATA version 13 (STATA Corp.; College Station, TX, USA) was used for performing the statistical analyses. Statistical significance was set at <0.05.

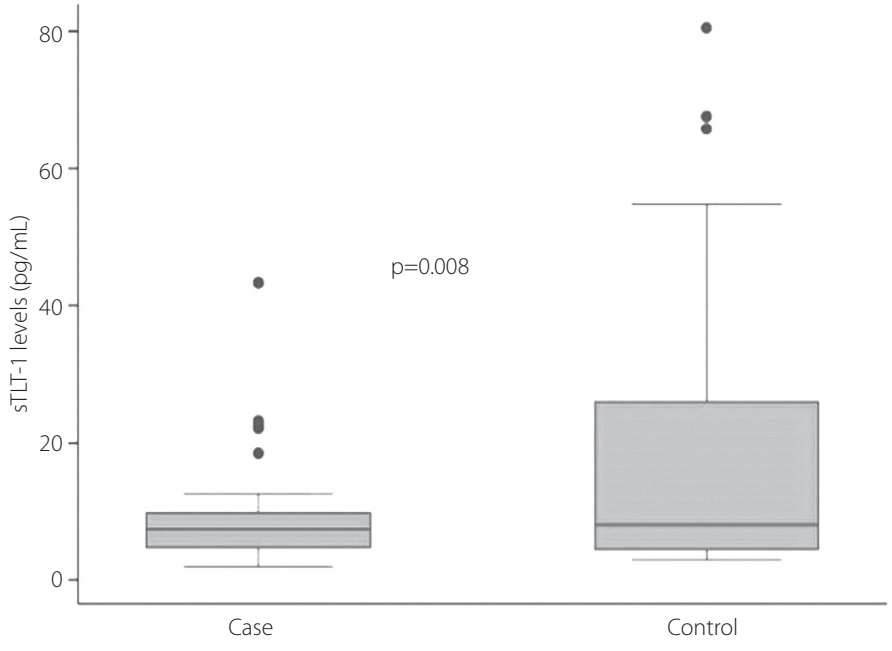

Figure 1. Plasma sTLT-1 levels in patients with systemic lupus erythematosus and healthy individuals

Table 1. Association of sTLT-1 levels with clinical manifestations and comorbidities

Feature	sTLT-1 levels pg/mL (SD)		
	Feature Present	Feature Absent	p
ACR SLE manifestations			
Malar rash (n=30)	7.8 (4.6)	11.3 (10.3)	0.273
Photosensitivity (n=37)	8.5 (5.5)	11.0 (12.3)	0.782
Oral ulcers (n=12)	10.3 (7.3)	8.5 (7.3)	0.462
Arthritis (n=30)	7.9 (5.1)	11.0 (10.0)	0.327
Serositis (n=6)	10.1 (6.3)	12.8 (16.0)	0.600
Pleuritis (n=4)	6.8 (1.9)	9.2 (7.5)	0.711
Pericarditis (n=2)	16.7 (7.7)	8.7 (7.1)	0.128
Renal disorder (n=20)	9.8 (9.4)	8.4 (5.1)	0.765
CNS involvement (n=4)	6.1 (3.4)	9.3 (7.5)	0.413
Hemolytic anemia (n=6)	9.4 (6.9)	8.9 (7.4)	0.896
Leukopenia (n=19)	7.9 (4.6)	9.7 (8.6)	0.850
Lymphopenia (n=39)	8.9 (7.2)	9.6 (7.9)	0.802
Thrombocytopenia (n=8)	6.4 (2.1)	9.6 (7.8)	0.317
ANA (n=46)	8.1 (5.0)	-	-
Anti-dsDNA antibodies (n=28)	8.4 (5.4)	12.3 (12.2)	0.426
Anti-Smith antibodies (n=12)	8.8 (5.1)	7.6 (5.1)	0.544
Antiphospholipid antibodies (n=15)	6.4 (2.6)	10.3 (8.4)	0.122
Other SLE manifestations			
Raynaud's phenomenon (n=30)	8.8 (8.2)	9.3 (5.2)	0.197
Comorbidities			
Diabetes mellitus (n=4)	7.5 (3.6)	9.1 (7.5)	0.671
Arterial hypertension (n=23)	8.9 (6.2)	9.1 (8.3)	0.930
Arterial vascular events (n=2)	15.8 (9.4)	8.7 (7.1)	0.176
Venous thrombosis (n=3)	7.1 (2.4)	9.1 (7.5)	0.647
Hypothyroidism (n=11)	7.5 (5.9)	9.5 (7.6)	0.434

SD: Standard deviation; ACR: American College of Rheumatology; SLE: Systemic lupus erythematosus; CNS: Central nervous system; ANA: Antinuclear antibodies

Table 2. Association of sTLT-1 levels with pharmacologic treatment in SLE patients

Feature	sTLT-1 levels pg/mL (SD)		
	Feature Present	Feature Absent	p
Treatment			
Corticosteroids (n=23)	11.1 (8.8)	6.9 (4.6)	0.014
NSAIDs (n=8)	11.4 (13.2)	8.5 (5.4)	0.954
Hydroxychloroquine (n=40)	9.3 (7.7)	6.8 (2.2)	0.568
Mycophenolate mofetil (n=1)	10.1 (6.4)	8.7 (7.5)	0.562
Azathioprine (n=4)	6.9 (2.2)	9.2 (7.5)	0.697
ACE inhibitors/ARB (n=15)	11.0 (6.7)	8.0 (7.4)	0.185
Statins (n=9)	8.2 (2.6)	9.2 (8.0)	0.398
Aspirin (n=6)	7.1 (2.5)	9.3 (7.7)	0.845

SD: Standard deviation; NSAIDs: non-steroidal anti-inflammatory drugs; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blockers

Results

A total of 46 patients with SLE and 28 healthy individuals were studied. No significant differences were found between patients with SLE and healthy controls for gender (93.5% vs. 92.9% women) and mean age (45.5±11.8 vs. 37.3±12.1 years). Disease duration for patients with SLE was 10.7± 4.1 years. As noted in Figure 1, patients with SLE had significantly decreased sTLT-1 plasma levels when compared with healthy subjects (9.0±7.2 pg/mL vs. 18.6±22.3 pg/mL, p=0.008).

Table 1 depicts the association between sTLT-1 levels and lupus manifestations and comorbidities in patients with SLE. We found no associations with clinical or serologic features of SLE. Likewise, no associations were found between sTLT-1 levels and selected comorbidities.

As shown in Table 2, we found that patients with SLE taking corticosteroids had significantly higher sTLT-1 levels than unexposed patients (11.1±8.8 pg/mL vs. 6.9±4.6 pg/mL, p=0.014). No associations were found for NSAIDs, hydroxychloroquine, mycophenolate mofetil, azathioprine, ACE inhibitors/ ARB, statins, and aspirin.

The relationship of sTLT-1 levels with disease activity, damage accrual, and PROs is shown in Table 3. A negative correlation tendency was observed between sTLT-1 levels and disease activity as measured using the SLAM-R (r=-0.278, p=0.064) and the lupus symptoms (r=-0.388, p=0.055) and physical health (r=-0.382, p=0.060) domains of LupusPRO. Furthermore, a significant negative correlation was found for the cognition domain (r=-0.442, p=0.027) and a positive correlation for the desires/goals domain (r=+0.435, p=0.030) of LupusPro. No correlation was found for damage accrual.

Discussion

We studied the clinical relevance of sTLT-1 in SLE. We found that when compared with healthy individuals, patients with lupus had significantly lower sTLT-1 levels. In patients with SLE, those exposed to corticosteroid treatment had higher sTLT-1 levels. We also found a negative trend between sTLT-1 levels and disease activity (per SLAM-R) and significant associations with PROs.

It has been proposed that sTLT-1 is a competitive inhibitor of the TREM-1 receptor family and thus decreases the intracellular signaling that mediates the amplification of inflammatory cytokines and chemokines (12). Also, it modulates the activation of lipopolysaccharide-induced neutrophil/monocyte and platelet-neutrophil

Table 3. Association of sTLT-1 levels with disease activity, damage accrual and patient reported outcomes

Feature	Correlation with sTLT-1 levels	
	r	p
SLAM-R	-0.278	0.064
SDI	0.002	0.991
LupusPRO domains		
Lupus symptoms	-0.388	0.055
Cognition	-0.442	0.027
Lupus medications	-0.313	0.128
Procreation	-0.071	0.736
Physical health	-0.382	0.060
Pain vitality	-0.300	0.145
Emotional health	-0.294	0.154
Body image	-0.153	0.467
Desires/goals	+0.435	0.030
Social support	-0.224	0.282
Coping	-0.319	0.121
Satisfaction with care	-0.191	0.361

SLAM-R: Systemic Lupus Activity Measure-Revised; SDI: Systemic Lupus International Collaborating Clinics (SLICC) Damage Index; LupusPRO: Lupus Patient-Reported Outcome

crosstalk, resulting in the decreased expression of TNF-α, IL-6, and IL8. Consequently, a deficiency of this peptide in patients with lupus may lead to increased TREM-1 signaling that results in the over-production of pro-inflammatory molecules. Thus, further research is required for addressing this potential mechanism.

The proposed pathogenic model is consistent with the clinical outcomes and PROs observed in our study. A negative trend was noted between sTLT-1 levels and disease activity. Furthermore, PROs, which are directly influenced by disease activity such as lupus symptoms, cognition, and physical health, were found to be negatively associated with sTLT-1 levels. Also, in agreement with these findings, sTLT-1 levels were positively associated with better patient's desires and goals as measured by LupusPRO.

Regarding pharmacologic treatments in our SLE population, corticosteroids were associated with higher sTLT-1 levels. This finding is in line with the mechanism of action of corticosteroids. It is well established that these immunosuppressive agents downregulate the transcription of pro-inflammatory proteins and upregulate those with anti-inflammatory properties (18).

Even though sTLT-1 levels have been associated with DIC, sepsis (12), platelet-endothelial cell interaction (19), and atherosclerotic disease (14), we did not find any association of sTLT-1 with thrombocytopenia, antiphospholipid antibodies, arterial vascular events, and venous thrombosis. Nevertheless, the lack of association could be explained by the small sample size and the relatively low prevalence of these vascular disorders in our study group.

Our findings are consistent with those of other studies regarding TREM receptor signaling in the pathogenesis of SLE. As already proposed by Derive et al. (12), sTLT-1 and sTREM-1 behave in the same manner, but sTLT-1 causes a decrease of pro-inflammatory cytokine production. In contrast to our findings, sTREM-1 plasma levels have been found to be increased in SLE, and it has also been positively associated with disease activity as per Systemic Lupus Erythematosus Disease Activity Index (9). Therefore, we can propose that sTLT-1 suppresses pro-inflammatory cytokines, while sTREM-1 increases the transcription of these cytokines. It will be interesting to measure both soluble counterparts of these receptors to assess the correlation between both peptides and their pathogenesis in SLE.

Our study has some limitations that need to be addressed. First, the sample size of our population was relatively small, which limited our ability to perform robust estimations leaving the analysis without sufficient power to detect significant differences. Prospective studies are required to increase the sample to a level that allows the evaluation adjusting for potential confounders and other variables of interest. Second, this is a cross-sectional study; therefore, sTLT-1 levels were measured at a specific time and not serially to allow the observation of trends through time. Third, the association of sTLT-1 levels with disease activity could not be clearly assessed because most of our patients had a relatively low disease activity at study visit. Nevertheless, we observed a trend between these variables. Further studies should compare sTLT-1 levels in patients with SLE with active and controlled disease. Lastly, information regarding treatment adherence was not assessed, and this could affect sTLT-1 levels and its association with pharmacological treatment. Nevertheless, this investigation approaches an uninvestigated topic, and promotes further research for the understanding of SLE pathogenesis.

In summary, to the best of our knowledge, this is the first study that measures sTLT-1 levels in patients with SLE. We found that patients with lupus have lower sTLT-1 levels compared with healthy individuals. Also, a negative correlation was observed for disease activity and some domains of LupusPRO. These findings highlight the importance of sTLT-1 and its anti-inflammatory properties and show that the deficiency of this protein could play an important role in the pathogenesis of SLE. Further studies are required to explore the potential role of this molecule and its inhibitory effect of the TREM family in the context of SLE.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of the UPR-MSC Human Research Protection Office (protocol #7510112).

Informed Consent: Subjects who were unable to comprehend the informed consent form pregnant women, and those with recent infections (within one month of the study visit) were excluded.

Peer-review: Externally peer-reviewed.

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