Inflammation, Vol. 36, No. 6, December 2013 (© 2013)
DOI: 10.1007/s10753-013-9694-z

Serum Soluble Triggering Receptor on Myeloid Cells-1 (sTREM-1) is Elevated in Systemic Lupus Erythematosus but does not Distinguish Between Lupus Alone and Concurrent Infection

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Abstract—We sought to determine serum triggering receptor expressed on myeloid cell-1 (sTREM-1) level in a cohort of patients with systemic lupus erythematosus (SLE). Serum sTREM-1 level of 98 patients with SLE and 49 healthy controls was assayed by ELISA. Serum sTREM-1 level was significantly elevated in a cohort of 78 unselected consecutively recruited patients with SLE (mean 1.1±2.8 ρg/ml, median 0.02 ρg/ml) compared to that of the controls (mean 0.11±0.3 ρg/ml, median 0 ρg/ml; $p<0.0001$). We also determined serum sTREM-1 level of 20 SLE patients with a concurrent infection (mean 0.6±1.1 ρg/ml, median 0.12 ρg/ml) and found it not statistically significant compared with that of the patients without infection. Serum sTREM-1 level did not correlate with SLE disease activity. Our finding of elevated serum sTREM-1 level suggests an increased shedding of TREM-1 in SLE and a possible novel pathway of innate immune response in autoimmunity.

KEY WORDS: soluble triggering receptor expressed on myeloid cells-1 (sTREM-1); systemic lupus erythematosus; innate immunity; infection; toll-like receptor 9.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune multisystemic disease of unknown etiology where innate immune activation plays a role in the initiation and augmentation of the autoimmune response [1]. SLE affects multiple organs including the skin, joints, lung, kidney, and brain that eventually leads to organ failure and premature death [2].

The innate immune system comprises pattern recognition receptors that regulate antigen presentation and subsequent response of the adaptive immune system (B and T cells). The toll-like receptors (TLRs) family of pattern recognition is largely responsible for mediating the activation of macrophages by exogenous pathogens and is associated with the pathogenesis of infectious and autoimmune diseases [3]. TLR9 is localized in the endoplasmic reticulum and recognizes internalized microbial DNA with unmethylated CpG motifs that directly activates macrophages through increased expression of metalloproteinase (MMP)-9 and activation of NFκB signaling pathway [4]. TLR9 is expressed by B cells of humans and mice and has been implicated in the breakdown of immunologic tolerance to self-nucleic acids in SLE and the generation of anti-dsDNA and anti-chromatin antibodies. Animal studies of SLE have implicated that TLR9 plays a crucial role in the pathogenesis of SLE [5, 6]. Formation of anti-dsDNA autoantibody was mediated by activation of TLR9 [5] that leads to the production of a variety of proinflammatory cytokines and type I interferon (IFN) [7]. However, the role of TLR9 is still controversial in lupus [8]. Christensen *et al.* [5] and Barrat *et al.* [9] showed that inhibition of TLR9 resulted in reduction of autoantibody production and amelioration of disease activity, and studies

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from two other groups suggested that TLR9 might play a protective role against lupus [10, 11]. Thus, the precise roles of TLR9 in autoimmunity may be more complex.

Triggering receptor expressed on myeloid cell-1 (TREM-1) is a recently discovered cell surface molecule that has been identified on both human and murine neutrophils and mature monocytes [12, 13]. It is a 30-Kd immunoglobulin superfamily member which is upregulated by lipoteichoic acid and lipopolysaccharide (LPS) and activates downstream signaling pathways in association with an adaptor protein called DAP12 [12–14]. TREM-1 binding to its still unidentified ligand synergizes the effects of LPS and amplifies the synthesis of proinflammatory cytokines and was shown to be associated with grave outcome in humans as well as in murine model of sepsis [15, 16].

Together with an upregulation of TREM-1 expression on the cell surface, a soluble form of this protein (sTREM-1) has been shown to be released during human sepsis [16]. Soluble TREM-1 might pose an anti-inflammatory effect following an infection as suggested by its inverse correlation with TNFα and IL-1β level in murine sepsis and it's protective effect in mouse model of sepsis [17]. Recently, TREM-1 upregulation was demonstrated in synovial fluid and cells of patients with rheumatoid arthritis (RA) as well as in the murine model of RA (collagen-induced arthritis, CIA) [18]. Moreover, blockade of TREM-1 using a recombinant adenovirus encoding extracellular domain of TREM-1 or a synthetic TREM-1 antagonistic peptide resulted in a significant amelioration of synovial inflammation in mice with CIA [19].

We have recently demonstrated a novel CpG-oligodeoxynucleotide (CpG-ODN)-induced TLR9 pathway for the regulation of macrophage TREM-1 expression and MMP-9-mediated TREM-1 shedding [20]. We have studied the *in vitro* effect of CpG-ODN-induced TLR9 activation on macrophage TREM-1 expression and shedding in mouse peritoneal macrophages and mouse macrophage cell line RAW 264.7 and found that while macrophage TREM-1 expression was not altered by CpG-ODN alone, macrophage stimulation with both LPS and CpG-ODN significantly abrogated TREM-1 LPS-induced membrane upregulation. Moreover, we found that CpG-ODN-induced TLR9 activation either alone or in combination with LPS resulted in a significant increase of supernatant sTREM-1 level. The release of sTREM-1 was found to be positively correlated with MMP-9 activity and was inhibited by chloroquine (an inhibitor of TLR9). Thus, our results suggest a novel mechanism for the regulation of macrophage TREM-1 expression mediated through CpG-ODN binding to TLR9 and a possible anti-inflammatory mode of action of CpG-ODN through MMP-9-mediated sTREM-1 shedding.

In light of the effects of sTREM-1 in infectious as well as in autoimmune diseases [16–19], we hereby present the results of a prospective case–control study of sTREM-1 serum level in a cohort of consecutively recruited patients with SLE including patients who presented with lupus-associated fever or infection-associated fever. Our pre-test hypothesis was that an elevated sTREM-1will be associated with a coincident infection in an attempt to differentiate between infection and lupus flare. We show that serum sTREM-1 level is significantly elevated in patients with SLE irrespectively of the presence or absence of infection or fever and suggest that increased shedding of TREM-1 occurs in SLE and might play a role in the pathogenesis of autoimmune disorders such as lupus.

PATIENTS AND METHODS

Study Sample

The study group comprised 78 consecutive patients with SLE followed at the Lupus Clinic of Rabin Medical Center, Petach Tikva, Israel, a university-affiliated hospital, and 20 patients with SLE who were hospitalized in the same center because of fever due to an infectious illness. All 98 patients fulfilled the criteria for SLE of the American College of Rheumatology [21]. Forty-nine healthy age- and sex-matched individuals served as the control group.

The study was approved by our Institutional review board, and all patients and controls signed an informed consent form.

All enrolled patients were systematically interviewed and physically examined for symptoms and signs related to SLE. Laboratory tests included erythrocyte sedimentation rate (ESR), C-reactive protein, complete blood count, serum creatinine, complement (C_3, C_4), anti-dsDNA antibody (by Farr assay, normal value <20 %), and urine sediment. The patients with a concomitant fever or infection were thoroughly examined to determine the presence, site, and cause of infection, including chest X-ray and blood, urine, and throat cultures. Infection was determined to be the cause of fever if the following were present: signs and symptoms of infection that was coincident with the fever and the fever and the signs and symptoms of the infection resolved with specific antimicrobial therapy if the infection was caused by bacteria or spontaneously and/or antiviral therapy if the infection was caused by virus. SLE was

determined to be the cause of fever if all the following were present: no evidence of an infectious cause, including negative blood and urine cultures, no evidence on chest X-ray and urinalysis for infection, and an illness typical of active SLE. Overall disease activity in both groups was scored with the SLE Disease Activity Index (SLEDAI) [22]. Serum was collected from venous blood drawn for the above laboratory tests and kept at −70 °C until assayed.

Determination of sTREM-1 Serum Level

Serum level of sTREM-1 was determined with a commercial enzyme-linked immunosorbent assay (ELISA) (DuoSet ELISA kit, human TREM-1, catalog number: DY1278, R&D Systems, Inc., Minneapolis, USA) on C96 MaxiCorp immunoplates (Cat. No. 430341, Nunc, Roskilde, Denmark) as follows. (1) The plates were coated overnight at 4 °C with mouse anti-human TREM-1 (4 μg/ml–100 μl per well) diluted in phosphate-buffered saline (PBS), pH 7.4. (2) The plates were washed three times with 200 μl PBS-Tween 20 (0.05 %), pH 7.4, and then 300 μl of blocking solution, including 1 % bovine serum albumin (BSA) in PBS, pH 7.4, kept for 2 h at room temperature, were added to each well to block nonspecific binding. (3) The wells were washed, and 100 μl of sera and standards (recombinant human TREM-1) in 1 % BSA in PBS, pH 7.4, were added and incubated overnight at 4 °C. (4) The wells were washed five times, and 100 μl of 1 % BSA in PBS, pH 7.4 containing biotinylated goat anti-human TREM-1 (400 ng/ml) was added. (5) After incubation for 2 h at room temperature, the wells were washed, and 100 μl streptavidin conjugated to horseradish peroxidase (1:200) was added, and the mixture was incubated for 20 min at room temperature. (6) After washing, 100 μl volume of substrate TMB (DAKO Corporation, CA, USA) in citric acid buffer, pH 5, was added. (7) The reaction was stopped with 2 N H_2SO_4, and the absorbance was measured at 450 nm. The assay was linear, in the range of 31.3–4000 ρg/ml of antigen.

Statistical Analysis

Results of continuous variables are shown as mean ± standard deviation and median (due to the skewed distribution). Pearson correlation coefficient (r) and the significance for it (p) were calculated between the variables.

To compare the two groups of patients (SLE vs. control or SLE infectious vs. SLE noninfectious), parametric statistics (i.e., Wilcoxon test) were performed. To compare more than two groups, parametric analysis of variance was performed (Duncan's and Dunnett's multiple comparison options); Kruskal–Wallis test was also performed. A p value less than or equal to 0.05 was considered statistically significant.

RESULTS

Ninety-eight patients with SLE who fulfilled the criteria for SLE of the American College of Rheumatology [21] and 49 healthy individuals have been prospectively enrolled to the study. Twenty patients of the SLE group presented with fever due to an infectious cause: each of the four patients had pneumonia, upper respiratory tract infection, and urinary tract infection; three patients had sepsis; two had gastroenteritis; two had CMV infection; and one had infected leg ulcer. The characteristics of the study cohort are shown in Table 1. The mean SLEDAI score of all the SLE patients (infectious and noninfectious, $n=98$) was 6.8±5.4 and of the noninfectious patients only ($n=78$), 6.6±4.7. Serum sTREM-1 level in the entire SLE cohort ($n=98$) was significantly higher (0.7±2.1 ρg/ml) than that in the control group ($n=49$) (0.1±0.3 ρg/ml) ($p=0.02$). Similarly, the mean serum level of sTREM-1 was significantly higher in the noninfectious patients with SLE (mean 1.1±2.8 ρg/ml, median 0.02 ρg/ml) than that in the control group (mean 0.11±0.3 ρg/ml, median 0 ρg/ml) ($p<0.0001$ by Wilcoxon test).

We also assayed serum sTREM-1 level of 20 patients with SLE who had evidence of infection coincident with fever at the time their blood sample was drawn. Surprisingly, their serum sTREM-1 level was lower (0.6±1.1 ρg/ml, median 0.12 ρg/ml) than that of the 78 patients with SLE without an infection (1.1±2.8 ρg/ml, median 0.02 ρg/ml), but the difference did not reach statistical significance. Moreover, sTREM-1 level of the infectious patients was not significantly higher than that of the control group.

Nine patients in the noninfectious group had fever at the time of the study which was attributed to the flare of the disease, with no evidence of an infectious cause. Their mean serum sTREM-1 level was 2.9±3.7 ρg/ml compared to 0.8±2.3 ρg/ml in the other 69 patients with SLE who did not have fever and normal controls ($p=0.002$ by Duncan's multiple range test).

In the total group of patients with SLE ($n=98$), serum sTREM-1 level was positively correlated with

Table 1. Background and Clinical and Laboratory Characteristics of Study Patients

Characteristics	SLE patients (n=98)	Healthy controls (n=49)
Age (years)	39.9±12.0	48.2±9.9
sTREM-1 (mean ± SD, ρg/ml)	0.98±2.54*	0.11±0.3
Serum C_3 (mean ± SD, mg/dl)	95.9±35.3	–
Serum C_4 (mean ± SD, mg/dl)	23.1±13.1	–
Serum anti-dsDNA antibody (mean ± SD, %) (normal <20 %, Farr assay)	33.3±19.4	–
Erythrocyte sedimentation rate (mean ± SD, mm/h)	47.1±28.1	–
C-reactive protein (mean ± SD, mg/dl)	1.8±3.8	–
SLEDAI score (mean±SD)	6.8±5.4	–

sTREM-1 soluble triggering receptor expressed on myeloid cells-1, *dsDNA* double-stranded DNA, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index
*p<0.0001

elevated ESR (r=0.4, p=0.002) but not with either SLEDAI score or level of serum complement (C_3, C_4), C-reactive protein, or anti-dsDNA antibody.

DISCUSSION

The present study shows, for the first time, that the serum level of the soluble form of TREM-1, a cell surface molecule expressed on neutrophils and monocytes [12–16], is significantly increased in patients with SLE, regardless of the disease activity (measured by SLEDAI) or presence of a coincident infection. Surprisingly, serum sTREM-1 level in our cohort failed to differentiate between lupus patients with and without coincident infection as well as between lupus-related fever and infection-related fever.

TLR4 stimulation by bacterial products such as LPS induces upregulation of membrane-bound and soluble TREM-1 level and has a synergistic effect with LPS with respect to the synthesis of pro-inflammatory cytokines TNF-α and GM-CSF, together with an inhibition of IL-10 production and an immediate degranulation of neutrophilic granules resulting in the release of IL-8, respiratory burst, and phagocytosis [15–17]. The pre-test hypothesis of this study was that an elevated serum sTREM-1level can differentiate between infection and disease flare in SLE based on previous studies that have shown in animal models as well as in humans that TREM-1 upregulation occurs strictly in response to infections through LPS-mediated TLR4 activation [14–16]. Many studies have indicated that blood or body fluids sTREM-1 could be a valuable diagnostic biomarker for various infectious diseases [23–28] and predict survival and mortality of patients at the early stage of sepsis [28–30]. Our data suggest that in patients with SLE, serum sTREM-1 cannot differentiate between lupus-caused fever and infection-caused fever. Our data are in accordance with a previous study that showed similar synovial fluid sTREM-1 level in patients with septic arthritis and RA [31]. Whereas synovial fluid sTREM-1 was significantly higher in septic arthritis compared to gout, non-septic/non-RA inflammatory arthritis, and non-inflammatory arthritis, it was found greater in RA than in gout, non-septic/non-RA inflammatory arthritis, and non-inflammatory arthritis (p=0.002, p=0.001 and p<0.001, respectively) and was very similar to synovial fluid sTREM-1 levels in septic arthritis. In addition, other studies have shown an elevated blood level of sTREM-1 in patients with RA that correlated with disease activity [18]. Serum sTREM-1 was found elevated in inflammatory bowel disease (IBD; Crohn's disease and ulcerative colitis) compared to normal controls [32]. No substantial differences in sTREM-1 expression levels were found in patients with active vs. quiescent IBD. Our results of an elevated serum sTREM-1 in SLE are in accordance with the findings in RA and IBD that together suggest that there is an increased level of sTREM-1 in autoimmune disorders. As in patients with IBD, serum sTREM-1 in our cohort of patients with SLE did not correlate with disease activity. The lack of correlation of serum sTREM-1 in patients with coincident infection in our cohort of patients with SLE is in contrast to a recent Korean study that found a significantly higher level of sTREM-1 in lupus patients who had a concurrent infection as compared to patients with lupus flare and normal control [33]. Kim *et al.* have found a significantly higher sTREM-1 level in the infection lupus group than in the lupus flare group (median 109.9 ρg/ml vs. 48.0 ρg/ml, p=0.034) with the highest diagnostic value of infection in lupus patients obtained at the threshold value of 53.2 ρg/ml. Of note, the level of blood sTREM-1 in the healthy controls in our study was

heterogeneous (mean 0.11±0.3 ρg/ml; median 0 ρg/ml) similar to what has been described in another study [32], thus may suggest that serum sTREM-1 does not only reflect its modulation by inflammatory responses but could also be influenced by inherent or ethnic factors.

TLR9 is expressed by B cells of humans and mice and has been implicated in the breakdown of immunologic tolerance to self-nucleic acids in SLE and the generation of anti-dsDNA and anti chromatin antibodies [5, 6]. Human endogenous DNA-containing autoantibody immune complexes found in serum of patients with SLE activate plasmacytoid dendritic cells to produce cytokines and chemokines, mainly INF-α, through cooperative interaction between TLR9 and Fcγ-receptor IIa (CD32) [34]. The proportion of B cells and monocytes expressing TLR9 was found higher among patients with active SLE than among patients with inactive disease and the percentage of TLR9-expressing B cells correlated with the presence of anti-dsDNA antibodies [35]. We have recently shown that CpG-ODN-mediated TLR9 activation of mouse macrophages induced a marked elevation of sTREM-1 level that is mediated by metalloproteinase-9 and inhibited by chloroquine [20]. This novel pathway of regulation of TREM-1 release had not yet been shown in *in vivo* animal or human studies; however, it suggests a possible pathway for increased release of macrophage TREM-1 through TLR9 activation that might play a role in innate immune response in SLE. Previous studies in animal models have shown that TREM-1-derived peptides, designed to inhibit the interaction of TREM-1 and its unknown ligand, were protective in animal models of endotoxemia and sepsis [15, 16]. Moreover, blockade of TREM-1 using a recombinant adenovirus encoding extracellular domain of TREM-1 or a synthetic TREM-1 antagonistic peptide resulted in a significant amelioration of synovial inflammation in mice with inflammatory arthritis (CIA) [19]. Taken together, an increased TLR9-mediated release of TREM-1 might prove as a novel anti-inflammatory process in autoimmunity and might be used as a novel therapeutic strategy for the treatment of human autoimmune disorders such as SLE.

We conclude that soluble TREM-1 level is increased in SLE. Our findings together with our recent *in vitro* study on the regulatory effects of TLR9 activation on macrophage membrane expression and sTREM-1 release [20] suggest that elevated sTREM-1 level in patients with SLE reflects a possible novel pathway of TLR9-mediated activation of the innate immune system and that TREM-1 may play a pathogenic role in the interaction between the innate and adaptive immune systems in systemic autoimmune disorders.

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