Serum tumor necrosis factor-related apoptosis inducing ligand in juvenile-onset systemic lupus erythematosus

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Abstract: Objectives: Apoptosis is induced by binding of death receptor ligands, members of tumor necrosis factor (TNF) superfamily, to their cognate receptors. It is suggested that TNF-related apoptosis inducing ligand (TRAIL) is involved in pathogenesis of juvenile-onset systemic lupus erythematosus (JSLE). This study aimed to assess TRAIL concentrations in sera of JSLE children and to determine their potential relationship with disease activity, anti-dsDNA levels, neutropenia and renal involvement**. Methods**: Circulating levels of TRAIL were measured by ELISA in serum samples obtained from 40 JSLE patients (20 with active and 20 with inactive disease) and 20 controls. **Results:** The mean (SEM) serum TRAIL concentration in JSLE was 1750.7 [440.2] pg/ml. Serum TRAIL concentrations in patients were higher than those in controls ($p < 0.01$). Serum TRAIL concentrations for children with inactive disease (1854.8 [485.4] pg/ml) and those with activity (1646.6 [390.6] pg/ml) were statistically comparable. JSLE children with positive anti-dsDNA antibodies had significantly higher TRAIL levels (mean = 1846 [456] versus 1455 [325] pg/ml; $p < 0.05$). Serum TRAIL concentrations were significantly higher in class (III & IV) nephritis compared to class I & II nephritis (1970 [512] versus 1330 [331] pg/ml; $p < 0.01$). Serum TRAIL concentrations in patients with neutropenia were higher than those without neutropenia (1805 [505] versus 1516 [400] pg/ ml; $p = 0.042$] and in controls ($p = 0.024$).**Conclusions:** Our data indicate that an increased level of TRAIL is a feature of JSLE that correlates with disease activity, anti-dsDNA titers neutropenia, and lupus nephritis.
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1. Introduction

Apoptosis (programmed cell death) is an active physiological process that leads to the ordered destruction of cells without the release of intracellular contents into the extracellular environment (which would cause an inflammatory reaction and tissue damage). Apoptosis can be induced passively, through lack of essential survival signals, or actively, through ligand induced trimerization of specific death receptors of the tumor necrosis factor (TNF) receptor family, such as Fas, the TNF receptor, or the TNF-related apoptosis inducing ligand (TRAIL) receptor.

Apoptosis is fundamental to maturation and homeostasis of the immune system. Increased apoptosis may induce autoimmune conditions. (1) TRAIL, also called apoptosis-2 ligand (Apo2L) for its similarity in sequence, structure, and function to FasL/Apo1L, is a TNF superfamily (TNFSF) member designated TNFSF10. TRAIL was cloned from human heart atrium, peripheral blood lymphocyte, and placenta cDNA libraries based on its similarity to regions highly conserved in the TNFSF. TRAIL is a 281 amino acid, approximately 32 kDa, type II transmembrane protein expressed on the cell surface. It lacks a signal sequence, has a highly conserved and singly glycosylated C-terminal extracellular domain, a transmembrane domain, and a short N-terminal cytoplasmic domain. Like other members of the TNFSF, TRAIL also exists in a soluble form. (2)

TRAIL is expressed in fetal kidney, liver, and lung, as well as in adult

Colon, heart, kidney, lung, ovary, peripheral blood lymphocytes, placenta, prostate, skeletal muscle, small intestine, spleen, and thymus. TRAIL is variably expressed in tumor cell lines. (3) TRAIL might be involved in the pathophysiology of autoimmune

Diseases in general and systemic lupus erythematosus (SLE) in particular.

Kaplan et al., reported that increased expression of TRAIL and FasL found on activated T cells contributes to increased monocyte apoptosis in patients with SLE. (4) Furthermore increased mRNA for TRAIL and its decoy receptors (TRAIL-R3 and TRAIL-R4) was found in peripheral blood mononuclear cells (PBMC) from SLE patients. (5) Furthermore increased mRNA for TRAIL and its decoy receptors (TRAIL-R3 and TRAIL-R4) was found in peripheral blood mononuclear cells (PBMC) from SLE patients. [(6)]

It has still remained unclear whether there is a close relationship between TRAIL and juvenile-onset SLE (JSLE). To our knowledge, this is the first report investigating the association between the expression of TRAIL and JSLE during disease activity and quiescence. We ask whether serum levels of TRAIL correlate with disease activity, anti-dsDNA levels, neutropenia, and renal involvement in JSLE children.

2. Subjects and Methods

This case-controlled study was conducted over a period of 24 months from the first of January 2010 to the end of December 2011. ***The study was approved by the ethics committee of Ain Shams University.*** An informed consent was obtained from all participants (patients and controls) or their caretakers following explanation of the study before enrollment. The children were divided into the following groups:

Juvenile-Onset Systemic Lupus Erythematosus (JSLE):

Clinical data and serum samples for all children with JSLE, who were referred to the Pediatric Rheumatology Unit, Children's Hospital, Ain-Shams University, Cairo, Egypt, were stored consecutively in a computerized database. The children for our study were selected from this database. They were eligible for the study if they fulfilled at least 2 points according to the Boston Weighted Criteria for the Classification of SLE. [7] We included 20 consecutive JSLE patients with inactive disease, defined as the persistent absence of disease activity [SLE disease activity index (SLEDAI) < 5] over at least a four month period with no immunomodulating drug treatment or on a constant dose of an immunomodulating agent. The SLEDAI score was calculated for each patient. [8] In addition, the effect of disease activity in 20 JSLE patients with active disease was studied. Patients with active disease had to fulfill previously defined criteria. Patients had active disease if their score was ≥ 6. Low activity was considered with scores ≤ 15 while high activity with scores > 15. [9] In our study, the score ranged from 10-46 (mean ± SD = 21.68 ± 5.32).

Active lupus nephritis was defined according to Gonzalez-Crespo *et al.,* [10] by one of the following: > 5 red blood cells, > 5 white blood cells, or any cast (red blood casts, granular, tubular or mixed casts) per high power field in the urinary sediment, proteinuria > 500 mg / 24 hours or 3 plus (+++) if quantitation is not performed, serum creatinine > 110 µmol/l, or creatinine clearance < 74.4 ml/min. Patients with stable deterioration, but in remission of renal disease, were included as non-active. Kidney stones, urinary tract infections and other causes of nephritis were excluded. Infection episodes were defined on clinical grounds and confirmed by microbiological results.

Flares were defined according to Gilkeson and coworkers, [9] as an increase in the physician global assessment (PGA) of 2 or more. The PGA was graded on a scale of 0-3 and was the physician's subjective opinion of the disease activity at the time of patient visit, with "0" representing no activity, "1" mild activity, "2" moderate activity and "3" marked activity. Decrease in disease activity was determined as a return of PGA to baseline. Based on selection via the PGA, disease flares occurred in a number of different organ systems including skin, kidney central nervous system and others. Lupus flares in our study were: nephritis (n=9), cytopenias (n=9) cerebral vasculitis (n=5), cutaneous vasculitis (n=5), hepatitis (n=4) and serositis (n=4).

Control group: Twenty clinically healthy children age and sex-matched to JSLE patients were enrolled for the purpose of comparison of the laboratory data. They were 14 females (70%) and 6 males (30%), with a female to male ratio of 2.3:1. Their ages ranged from 6 to 16 years, with a mean age of 12.03 ± 2.01 years. They underwent general and systemic examination to exclude any current illness particularly collagen-vascular and rheumatic diseases, co-existing chronic inflammation, and cancers.

Study measurements:

1. **Quantitative determination of serum human TNF-Related Apoptosis-Inducing Ligand (TRAIL/TNFSF10):** This assay employs a quantitative sandwich enzyme immunoassay technique. Reagents were supplied by Quantikine® (R&D Systems, Inc. 614 McKinley Place N.E. Minneapolis, MN 55413 USA) (Catalog Number DTRL00). The minimum detectable dose (MDD) of human TRAIL ranged from 0.57-7.87 pg/ml. The mean MDD was 2.86 pg/ml.
2. Erythrocyte sedimentation rate (ESR; in mm/hour) 1St hour by Westergren method.
3. Quantitative measurement of serum anti-double stranded-DNA (Anti-dsDNA) antibodies by EIA *(anti-dsDNA Kit, Ortho Diagnostic, Raritan, NJ, USA), (Farr assay).*
4. Complement 3 and 4 (C3 & C4) using turbidimetry on Turbitimer (Turbiquant C3 and C4; Behringwerke Diagnostics GmbH, Marburg, Germany).
5. Serum and urinary creatinine (Cr) using a modified rate Jáffe method on Synchron CX7 autoanalyzer (Beckman Instruments, Brea, California USA). Calculation of creatinine clearance (Cr Cl) was done from the following equation: Creatinine clearance = urinary creatinine (mg/dl) x urinary volume (cc) x body surface area (m^2) /plasma C x 1.73
6. Complete urine analysis and measuring total 24 hours urinary proteins.

Statistical Analyses:

All statistical analyses were carried out using SPSS software for Windows system (version 11.5; SPSS Inc, Chicago, IL). Data are presented as mean (SEM). Differences in mean serum TRAIL levels between the patient groups and normal controls were determined by ANOVA and Bonferroni post hoc test (Gaussian distribution) and by the χ^2 test. The Spearman test was used to determine correlations. Student's t test was used to determine differences between serum TRAIL levels in males and females (control group). A probability (p) value of < 0.05 was considered significant.

3.Results

Characteristics of the JSLE patients and controls are given in table 1.

To evaluate whether serum TRAIL levels are influenced by sex or age, or both, we determined the correlation between serum TRAIL levels and age, and we analyzed the difference in serum TRAIL values between males and females in the control group. There was no difference in mean serum TRAIL concentrations between males (n = 6; 623.1 [74.3] pg/ml) and females (n = 14; 705.9 [65.4] pg/ml) (p = 0.45). There was also no correlation between age and serum TRAIL concentrations (r = 0.245, p = 0.21).

The mean (SEM) serum TRAIL concentration in the whole group of JSLE children was 1750.7 [440.2] pg/ml. Serum TRAIL concentrations in JSLE children were higher than those in healthy volunteers (p < 0.01). Serum TRAIL concentration was 1854.8 [485.4] pg/ml for children with inactive disease and 1646.6 [390.6] pg/ml for those with active disease. The difference between the two groups was not significant (p > 0.05). Worth mentioning, 87.5% of the whole JSLE children (35 of 40) had a mean serum TRAIL level above that of the healthy volunteers, at 664 [69.9] pg/ml. Of the 20 patients with inactive disease three had a serum level below the mean control value. In patients with active disease this was seen in two of the 20 patients (p = 0.05, χ^2 test) (Fig.1).

We examined the association between the levels of serum TRAIL and specific clinical manifestations of the disease (Fig.2). No clear relation was found between serum TRAIL concentrations and renal, cerebral, cutaneous, serosal, haematological, or hepatic manifestations. Patients with serositis seemed to have lower serum TRAIL levels, although numbers were small. Serum TRAIL levels correlated with biomarkers of disease activity (ESR and anti-dsDNA concentration) and SLEDAI score.

All children during disease activity showed significant positive correlations between serum TRAIL values and serum creatinine and 24 hours urinary protein excretion (p < 0.05). On the other side, serum TRAIL levels correlated inversely with the estimated creatinine clearance and serum C3 and C4 levels (p < 0.01).

JSLE children with positive anti-dsDNA antibodies had significantly higher serum TRAIL levels (mean = 1846 [456] versus 1455 [325] pg/ml; p < 0.05). Moreover, serum TRAIL levels correlated positively with anti-dsDNA autoantibodies titers (r = 0.632; p < 0.01; Fig.3).

Renal biopsy of JSLE children revealed predominance of class IV nephritis in (n = 6; 30%), next followed by class III (n = 7; 35%), then class II (n = 4; 20%), and the least common was class I (n = 3; 15%) according to WHO pathologic classification of lupus nephritis. Serum TRAIL concentrations were significantly higher in children with class (III & IV) nephritis compared to those with class I & II nephritis (1970 [512] versus 1330 [331] pg/ml; p < 0.01).

Leucopenia is seen in patients with active JSLE. As TRAIL can induce apoptosis in lymphocytes, monocytes, and neutrophils, we analyzed whether TRAIL levels were correlated with blood cell counts. Analyzing all patients, no correlation was found between serum TRAIL concentration and monocyte, lymphocyte, or leucocyte counts. However, when we focused on nine patients with neutropenia (<1.5 X 10^9 neutrophils/l) we found that the serum TRAIL concentrations in these patients tended to be higher than in JSLE patients without neutropenia (1805 [505] versus 1516 [400] pg/ ml; p = 0.042] and in healthy volunteers (p= 0.024). Moreover, serum TRAIL levels showed a significant negative correlation with neutrophil counts in JSLE children (r = - 0.551; p < 0.01; Fig.4).

Finally, we examined the relation between serum TRAIL concentrations and immunosuppressive drug treatment (prednisolone therapy and cyclophosphamide). No correlation between the use of these agents and TRAIL values was found (data not shown).

Table 1. Characteristics of the JSLE children and control subjects

Variable	Controls (n = 20)	Active SLE (n = 20)	Inactive SLE (n = 20)	p value active vs inactive
Age (years) (mean) (range)	12.03 (6-16)	12.5 (6-16)	10.7 (7-15)	> 0.05
Male/female	14/6	2/18	5/15	-
Duration of illness (years) (mean)	-	4 (1-7)	3.5 (2-6)	> 0.05

(range)				
Renal disease	-	9	-	-
Central nervous system disease	-	5	-	-
Serositis	-	4	-	-
Haematological disease	-	9	-	-
Skin involvement	-	5	-	-
Hepatic involvement	-	4	-	-
SLEDAI	-	13.86 (2.95)	2.79 (0.65)	0.0001*
Prednisolone	-	3	13	-
Cyclophosphamide	-	5	2	-
Prednisolone + Cyclophosphamide	-	12	5	-
Anti-dsDNA (IU/ml)	10.83 (2.4)	175.2 (62.69)	14.65 (2.9)	0.011*
C3 (mg/dl)	102.7 (54)	51.4 (11)	98.2 (7)	0.025*
C4 (mg/dl)	25.8 (9.58)	9.4 (1.2)	18.8 (3.5)	0.029*
ESR (mm/hour)	9.59 (4.16)	65.45 (14.98)	11.52 (2.56)	0.0004*
Leucocytes ($x10^9$/l)	6.03 (0.90)	4.86 (0.51)	5.20 (0.40)	0.17
Neutrophils ($x10^9$/l)	3.08 (0.98)	2.91 (0.48)	3.66 (0.56)	0.56
Monocytes ($x10^9$/l)	0.39 (0.032)	0.25 (0.04)	0.46 (0.039)	0.19
Lymphocytes ($x10^9$/l)	2.99 (1.48)	0.91 (0.19)	1.41 (0.18)	0.29
Serum creatinine (mg/dl)	0.6 (0.032)	1.6 (0.098)	0.7 (0.054)	0.032*
Estimated creatinine clearance (ml/min)	119.5 (29.15)	59.28 (12.35)	89.85 (19.11)	0.012*
24 hours urinary protein excretion (gm/day)	0.26 (0.087)	2.8 (0.72)	0.4 (0.097)	0.041*
TRAIL (pg/ml)	664 [69.9]	1646.6 (390.6)	1854.8 (485.4)	0.45

Values are mean (SEM) or number, unless stated.
*Significant *p* values.

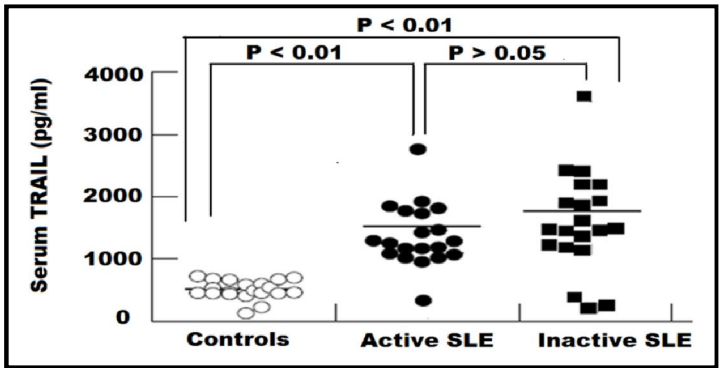

Figure 1. Serum TNF related apoptosis inducing ligand (TRAIL) concentrations (pg/ml) in JSLE children with inactive disease (n = 20), JSLE children with active disease (n = 20) and healthy controls (n = 20). The horizontal lines give the mean TRAIL value.

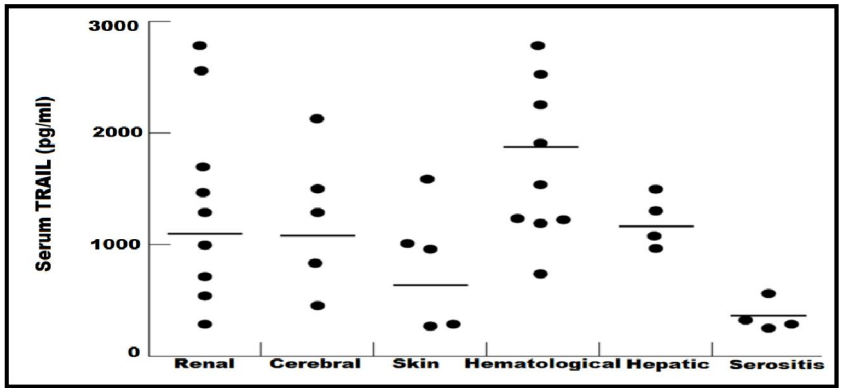

Figure 2. Serum TNF related apoptosis inducing ligand (TRAIL) concentrations (pg/ml) in JSLE children who had active disease (n = 20) divided by clinical disease manifestations (n = 36). One patient could have different manifestations of JSLE; thus 36 disease manifestations were found in 20 patients. The horizontal lines give the mean TRAIL value.

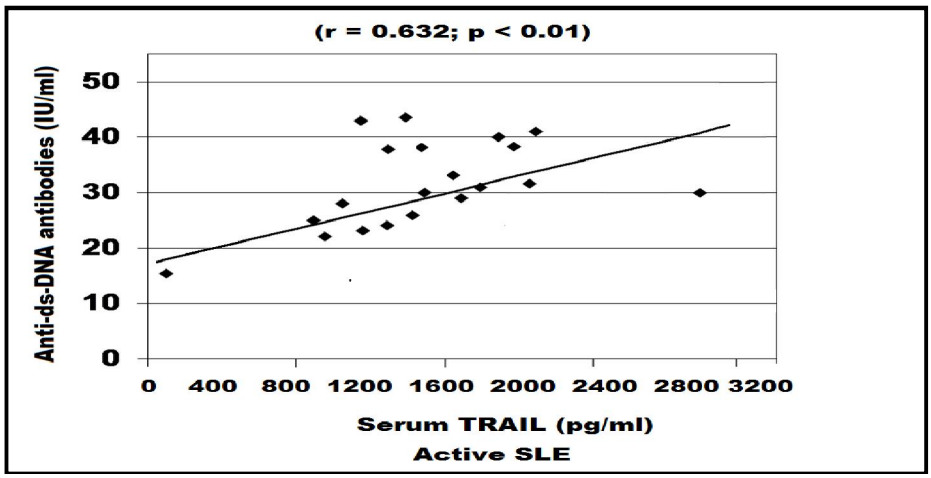

Figure 3. Significant positive correlation between serum TNF related apoptosis inducing ligand (TRAIL) (pg/ml) levels and serum anti-dsDNA antibodies (IU/ml) in JSLE during disease activity.

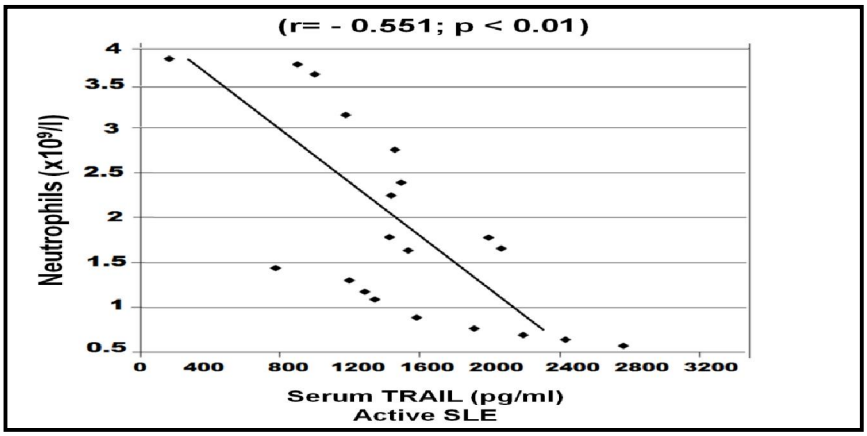

Figure 4. Significant negative correlation between serum TNF related apoptosis inducing ligand (TRAIL) (pg/ml) levels and neutrophil count (x10^9/l) in JSLE during disease activity.

4. Discussion

Increased neutrophil, monocyte, and lymphocyte apoptosis is a feature of SLE pathophysiology. The Fas/FasL system contributes to increased apoptosis. [11] The importance of the other death pathways and the role of the apoptosis inducing ligands of the TNF family and their death receptors are, however, uncertain. Recent interest had focused on TRAIL, and its involvement in the pathophysiology of human autoimmune diseases including Sjögren's syndrome, [12, 13] systemic sclerosis, [14] ankylosing spondylitis [15] and primary biliary cirrhosis. [16]

Although the implications of TRAIL in adult-onset SLE had been reported before, [6, 11, 17-19] the novelty of this study is the use of a pediatric patient group and comparison of TRAIL levels during flare and quiescence.

Results of this study confirm the importance of TRAIL in JSLE pathophysiology. JSLE children had higher serum TRAIL concentrations in comparison to healthy volunteers. It was of interest that serum TRAIL concentrations in children with active and quiescent disease were statistically comparable. This finding is contradictory to the report of Rus *et al.* [18] As TRAIL has an extremely short calculated half life of only 30 minutes, this indicates continuous TRAIL production or secretion. Moreover, peripheral blood lymphocytes (PBL) are activated in JSLE children even during clinically inactive disease.

TRAIL may modulate cell survival and proliferation through interaction with 2 death receptors (DRs), DR4 (TRAIL receptor 1 [TRAIL-R1]) and DR5 (TRAIL receptor 2 [TRAIL-R2]), and the actions of TRAIL are regulated by three decoy receptors, 2 DcRs, DcR1 (TRAIL-R3) and DcR2 (TRAIL-R4) and osteoprotegerin. TRAIL-R1 and 2 contain an intracellular motif called the "death domain" that subsequently activates caspase-8 that leads to apoptosis. Enhanced reactivity of T cells to auto-antigens as a result of TRAIL-induced co-

stimulation may play a pathophysiological role in the development of JSLE.

A question remains about the origin of increased serum TRAIL levels in JSLE children. PBL are activated in JSLE children even during clinically inactive disease. TRAIL engagement selectively activated human CD4, rather than CD8, T cells and augmented IFN-γ production via a p38 MAPK-dependent pathway. Activation of p38 MAPK was detected after TRAIL-induced T cell activation. T cells isolated from patients with SLE demonstrated a stronger response to TRAIL-induced co-stimulation, in terms of proliferation and increased up-regulation of CD25 after activation, when compared with T cells from healthy subjects. [20] *In vivo*, T cell activation has been found to contribute to increased expression of TRAIL and other apoptotic ligands on lupus T cells isolated from SLE patients. *In vitro*, furthermore, TRAIL could be released from activated T cells as well as from stimulated monocytes. These findings are supported by increased gene expression of TRAIL and its decoy receptors in PBMC from SLE children. [18] This over expression could result in increased TRAIL concentrations.

Interferons (IFN-α, β, andγ) might also play an important role. Over expression of IFN induced genes occurs in PBMC of pediatric SLE patients. [21] This is of interest as human monocytes rapidly express TRAIL following activation with IFN-α and IFN-γ. [22]

Increased concentrations of TRAIL may be explained also by immunosuppressive drugs, which are known to induce apoptosis. This could subsequently lead to TRAIL release from apoptotic cell fragments. For this reason we examined the relation between TRAIL concentrations and the use of immunosuppressive drugs (prednisolone and cyclophosphamide). We did not find a clear correlation in this small patient population, which excludes a substantial influence of drugs.

Neutropenia, a common laboratory finding in SLE, was first described more than 70 years ago and was found in about 50%-60% of patients with SLE. [23] Neutrophil apoptosis is increased in JSLE [24, 25]. Dysregulated neutrophil apoptosis may result in the development of autoimmune disease by contributing to nuclear autoantigen exposure, leading to autoantibody generation and a breakdown in immune tolerance. TRAIL could accelerate neutrophil apoptosis. [26] However, the exact role of TRAIL and molecular mechanisms of JSLE neutropenia has not been fully explained. In this study, we examined whether TRAIL is involved in the pathogenesis of JSLE neutropenia using samples from JSLE children. Serum TRAIL levels in JSLE children with neutropenia were significantly higher than those of JSLE children without neutropenia and healthy volunteers. Serum TRAIL levels showed a significant negative correlation with neutrophil counts in JSLE children. Our data are largely in accord with other reports. [11, 17]

Matsuyama *et al.* [17] reported expression of TRAIL-R2 and 3 on PMN cell surface and suggested that these receptors contribute to the maintenance of the balance of PMN apoptosis. The expression of TRAIL-R3 was significantly lower in SLE patients with neutropenia than in patients without neutropenia or in healthy volunteers, and treatment with glucocorticoids negated the decrease of TRAIL-R3 expression on neutrophils. In addition, autologous T cells of SLE patients, which express TRAIL on surface, may kill autologous neutrophils. Therefore, we believe that TRAIL is involved in the molecular mechanism of neutropenia and may accelerate neutrophil apoptosis in JSLE.

Individuals with SLE show evidence of a significant increase in monocyte apoptosis. This process is mediated, at least in part, by an autoreactive T cell subset that kills autologous monocytes in the absence of nominal antigen. [5, 6]

Binding of TRAIL to its death receptors TRAIL-R1 and 2 can accelerate apoptosis of monocytes and lymphocytes induced by T cells in SLE. Kaplan and coworkers, [5] reported that expression of the apoptotic ligands TRAIL, TNF-like weak inducer of apoptosis (TWEAK), and Fas ligand on lupus T cells mediate autologous monocyte death induced by lupus T cells and that this cytotoxicity is associated with increased expression of these molecules on activated T cells, rather than with an increased susceptibility of lupus monocytes to apoptosis induced by these ligands. This is supported by decreased monocyte and lymphocyte counts found in our children with active SLE (Table1). We were, however, unable to find a correlation between serum TRAIL levels and these cell counts in children with JSLE. Probably because of the small number of children with monocytopenia and lymphopenia in our study, the relation we found did not reach significance.

Domains specific for JSLE activity were the immunological tests and the kidney function parameters. [27]

In our study, serum TRAIL levels correlated with SLEDAI score and biomarkers of disease activity (ESR and anti-dsDNA levels). JSLE children with positive anti-dsDNA antibodies had significantly higher serum TRAIL levels. Moreover, serum TRAIL levels correlated positively with the anti-dsDNA autoantibodies titers. Our results were in accord with Komatsuda *et al.* [6] however, contradictory to Lub-de Hooge *et al.* [11] This contradiction could be ascribed to the possibility that correlations were not

demonstrated owing to the relatively small number of patients with a very heterogeneous disease. SLE patients with increased antibodies to dsDNA had increased apoptotic neutrophils. Increased circulating apoptotic neutrophils in SLE correlate positively with disease activity and may contribute to autoantigen excess including dsDNA. [28]

Both TRAIL and their receptors are expressed by renal cells. Noteworthy, TRAIL has been recently linked to the pathogenesis of diabetic nephropathy through interactions with other cytokines and hyperglycemia and that tubular cells proinflammatory cytokines enhance TRAIL expression. [29] We postulated that serum TRAIL over expression might be related to the pathogenesis of lupus nephritis. Therefore, we sought to investigate serum TRAIL expression in relation to laboratory variables of renal involvement and histopathological grading results.

Serum TRAIL levels correlated with laboratory variables of renal involvement. Serum TRAIL concentrations were significantly higher in children with class (III & IV) nephritis compared to those with class I & II nephritis. Our data are in accord with Nguyen et al. [30] who reported TRAIL, DR4 and DR5 upregulation in proximal and distal tubules of patients with proliferative lupus nephritis. In vitro, expression of TRAIL, DR4 and DR5 on primary proximal tubular epithelial cells (PTEC) was induced by TNF-α and IFN-γ. Functionally, TRAIL did not induce apoptosis but rather enhanced the proliferation of PTEC through activation of PI3 kinase/AKT and ERK1/2, increased IL-8 production and upregulated ICAM-1 expression. It seems that TRAIL plays important roles in the pathogenesis of lupus nephritis, and that the expression of TRAIL correlates with the severity of interstitial kidney damage probably through cytokine induced upregulation of TRAIL, DR4 and DR5 in tubules from patients with proliferative lupus nephritis.

From this pilot study, our results indicate an important role for TRAIL in the pathogenesis of JSLE particularly in lupus nephritis and neutropenia. TRAIL-mediated apoptosis may amplify the abnormal apoptotic process in JSLE. However, the exact mechanism and significance of this remain to be elucidated in larger prospective studies. It seems that elevated TRAIL levels could serve not only as a potential marker of JSLE but correlate with disease activity and severity as well. A prospective longitudinal study is needed to investigate serum TRAIL values over time with respect to disease activity and immunosuppressive treatment. Investigation of TRAIL and TRAIL-R expression and function in tissues, and on monocytes and lymphocytes, in JSLE patients is also eagerly awaited.

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