Soluble E-cadherin in Systemic Lupus Erythematosus

Tao Jin, Katarina Almehed, Yihong Zhu, Hans Carlsten, and Helena Forsblad-d'Elia

ABSTRACT. ***Objective.*** E-cadherin is a potent adherens junction molecule implicated in tissue morphogenesis, epithelial functioning, and immune regulation. Serum levels of soluble E-cadherin (sE-cadherin), an end product of proteolytic cleavage of E-cadherin, is increased in patients with cancer, infections, and inflammation-related diseases. The aim of our study was to measure serum levels of sE-cadherin in systemic lupus erythematosus (SLE) and to determine associations between serum levels of sE-cadherin and markers of inflammation and organ damage in female patients with SLE.

Methods. Serum levels of sE-cadherin were analyzed by ELISA in 150 female patients with SLE and 31 healthy women. Simple and multiple regression analyses between sE-cadherin levels and disease-related variables were performed in patients with SLE.

Results. Serum levels of sE-cadherin were elevated in patients with SLE compared with levels in healthy controls. sE-cadherin levels correlated positively with age, disease duration, SLE Collaborating Clinics Damage Index, erythrocyte sedimentation rate (ESR), s-creatinine, cholesterol, triglycerides, interleukin 6, and matrix metalloproteinase-3. In multiple regression analysis, s-creatinine, age, ESR, and triglycerides remained determinants of sE-cadherin. Within the patients with SLE, higher sE-cadherin levels were found only in patients with renal damage, i.e., s-creatinine > 90 μmol/l, glomerular filtration rate < 50 ml/min, or renal involvement ever by SLE.

Conclusion. Our study demonstrates significantly elevated serum levels of sE-cadherin in women with SLE compared with healthy women. The levels of sE-cadherin were positively correlated to s-creatinine, age, ESR, and triglycerides. Significantly elevated sE-cadherin levels were observed only in patients with renal damage. (First Release Sept 1 2013; J Rheumatol 2013;40:1677–82; doi:10.3899/jrheum.130518)

Key Indexing Terms:
sE-CADHERIN SYSTEMIC LUPUS ERYTHEMATOSUS RENAL DAMAGE

E-cadherin is a transmembrane glycoprotein highly expressed at the surface of epithelial cells, mediating calcium-dependent homotypic cell-cell adhesion[1]. The cytoplasmic tail of E-cadherin forms a dynamic complex with catenins and regulates several intracellular signal transduction pathways[2]. E-cadherin is responsible for joining adjacent epithelial cells and safeguarding epithelial barrier function.

From the Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy; and the Department of Obstetrics and Gynecology, Sahlgrenska Cancer Centre, Institute of Clinical Sciences, University of Gothenburg, Göteborg, Sweden.

Supported by grants from The Health and Medical Care Executive Board of the Västra Götaland, Åke-Wiberg Foundation, Tore Nilsson Foundation, Rune och Ulla Amlövs Foundation for Rheumatology Research, Göteborg Association Against Rheumatism, Medical Society of Göteborg, Swedish Medical Society, and the Region Västra Götaland (agreement concerning research and education of doctors), and the Margareta Research Foundation.

T. Jin, MD, PhD, Associate Professor; K. Almehed, MD, PhD, Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg; Y. Zhu, MD, PhD, Department of Obstetrics and Gynecology, Sahlgrenska Cancer Centre, Institute of Clinical Sciences, University of Gothenburg; H. Carlsten, MD, PhD, Professor; H. Forsblad-d'Elia, MD, PhD, Associate Professor, Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg.

Address correspondence to Dr. T. Jin, Department of Rheumatology and Inflammation Research, Guldhedsgatan 10, S-413 46 Göteborg, Sweden. E-mail: tao.jin@rheuma.gu.se

Accepted for publication July 5, 2013.

Accumulating evidence suggests that E-cadherin also acts as an immunological regulator in addition to an adherens junction molecule[3]. Langerhans cells are able to form a dense dendritic cell (DC) network with the highly E-cadherin-expressing keratinocytes to cover the entire body surface by using E-cadherin[4]. Epidermal proinflammatory cytokines downregulate E-cadherin expression and attenuate E-cadherin mediated adhesion between those cells[5]. Bone marrow-derived DC are also known to exhibit high amounts of surface E-cadherin. Loss of E-cadherin-mediated adhesion activates the β-catenin signaling pathway in DC, which protects against experimental allergic encephalomyelitis in mice[6]. Indeed, ablation of β-catenin expression in DC enhanced inflammatory responses and inflammatory bowel disease in a mouse model[7]. In contrast, monocyte-derived inflammatory DC that express E-cadherin promote intestinal inflammation[8]. Besides its immune regulatory properties in DC, E-cadherin was identified as a marker for alternatively activated macrophages that were involved in homotypic and heterotypic interactions through interleukin (IL)-4 and E-cadherin/catenin complexes[9].

E-cadherin can be cleaved by several proteases such as matrix metalloproteinases (MMP), plasmin, kallikrein 7, and ADAM10[10]. This process is called E-cadherin ectodomain shedding, which results in the release of an

80-kDa soluble peptide fragment referred to as soluble E-cadherin (sE-cadherin). Loss of E-cadherin mediated adhesions is a well-known characteristic when epithelial tumors progress toward malignancy. Indeed, sE-cadherin has been suggested as a diagnosis/prognosis biomarker for several forms of cancer, e.g., gastric cancer[11,12], bladder cancer[13], prostate cancer[14], ovarian cancer[15], colorectal cancer[16], melanoma[17], and lung cancer[18]. Interestingly, sE-cadherin is upregulated not only in cancer, but also in different inflammatory conditions, e.g., sepsis[19], inflammatory skin diseases[20], pelvic inflammatory disease[21], and primary Sjögren syndrome[22]. To the best of our knowledge, serum levels of sE-cadherin have not been investigated in SLE. We hypothesize that E-cadherin shedding may also happen in other inflammatory rheumatic diseases.

The aim of our study was to (1) assess serum levels of sE-cadherin in women with SLE and compare the levels with healthy controls; and (2) investigate associations between serum levels of sE-cadherin and disease-related variables in SLE.

MATERIALS AND METHODS

Patients. All patients with SLE attending rheumatology clinics during the winter and spring of 2002-2003 in Göteborg and Borås, in western Sweden, were invited to participate in this cross-sectional study, as described[23]. The original aim of our study was to determine prevalence and risk factors of osteoporosis in women with SLE. One hundred fifty female patients fulfilling at least 4 of the 1982 American College of Rheumatology (ACR) classification criteria for SLE[24] were included in and completed the study. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) was used to score disease activity[25]. Disease damage was recorded according to the Systemic Lupus International Collaborative Clinics/ACR Damage Index (SLICC)[26]. Glomerular filtration rate (GFR) was calculated using the Cockcroft and Gault equation[27]:

$$\text{GFR (ml/min)} = (140 - \text{age}) \times \text{weight (kg)} \times 1.04/\text{S-creatinine } (\mu\text{mol/l})$$

Cumulative corticosteroid intake was calculated by reading the medical records of all patients. The same rheumatologist (KA) examined all patients and reviewed all medical records. The clinical data and materials were further analyzed in the current study to investigate serum levels of sE-cadherin in those patients.

Healthy controls. A control group of 31 healthy female staff members and PhD students (age range 25–63 yrs) in the Department of Rheumatology were analyzed for serum levels of sE-cadherin, MMP-3, and MMP-9. No significant correlation was found between serum sE-cadherin and age.

Laboratory tests. Serum from venous blood samples and urine were collected, aliquoted, and stored at –70°C until the analyses of sE-cadherin, MMP-3, and MMP-9 following standard routines for handling, processing, and storage of biosamples. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood (cell) count, creatinine, and complement factors (C3 and C4), were analyzed consecutively in the Department of Clinical Chemistry of Sahlgrenska University Hospital.

sE-cadherin and cytokines. The levels of sE-cadherin (in serum and urine), MMP-3, and MMP-9 in serum were determined using the specific sandwich ELISA kits (Quantikine; R&D Systems Inc.) according to the manufacturer's protocols. The detection threshold was 0.09 ng/ml for sE-cadherin, 0.045 ng/ml for MMP-3, and 0.312 ng/ml for MMP-9. Quantitative sandwich ELISA kits were also used for measurement of proinflammatory cytokines tumor necrosis factor-α, IL-1β, IL-6, and soluble IL-6 receptor (sIL-6R; Quantikine; R&D Systems Inc.) with detection limits of 0.12, 0.1, 0.7, and 6.5 pg/ml, respectively.

Ethical considerations. All patients gave informed consent prior to participation, and the study was approved by the regional ethics committee at the University of Gothenburg.

Statistical analysis. Analyses were performed using PASW statistics 18 (SPSS Inc.). All variables were tested with the Kolmogorov-Smirnov normality test. Statistical comparisons of sE-cadherin levels in sera among patients with SLE and healthy controls were made using an unpaired t test when the variables followed a normal distribution, or sample size in each group was > 30. Mann-Whitney U test was used when the variable followed a non-normal distribution and sample size in 1 group was < 30. Pearson correlation was used when the variables were normally distributed; otherwise, Spearman correlation was used. Significant variables were then entered in the multiple linear regression analyses as independent variables and serum levels of sE-cadherin as the dependent variable. A forward stepwise method was used. All tests were 2-tailed, and a $p < 0.05$ was considered statistically significant.

RESULTS

Demographic and disease-related variables. The participants' ages ranged from 20 to 82 years. Eighty-six (57%) were taking disease-modifying antirheumatic drugs (DMARD), and 79 (53%) were treated with glucocorticosteroids (mean dose of prednisolone 3.28 mg/day). Patients had the mean scores of 6.7 for SLEDAI and 2.9 for SLICC. The mean value of serum creatinine was 94.3 μmol/l. The calculated GFR was 73.2 ml/min on average. Only 1 person had endstage renal disease, but 9 (6.1%) had proteinuria over 3.5 g/24 h. Sixty-five patients (43.3%) had serum creatinine over 90 μmol/l, and 15 (10%) had a GFR of less than 50 ml/min by use of the calculated GFR value. More details of demographic and disease-related variables are in our previous publication[28], which used the same patient materials.

Elevated serum levels of sE-cadherin in patients with SLE. Table 1 shows the serum levels of sE-cadherin in 150 female patients with SLE and 31 healthy women. The patients with SLE did not differ significantly in age from the healthy controls (mean ± SD, 48.7 ± 12.7 vs 45.8 ± 11.3 yrs, respectively). sE-cadherin was elevated in patients with SLE as compared with healthy controls (93.3 ng/ml vs 80.6 ng/ml, $p < 0.05$).

Correlations between serum levels of sE-cadherin and disease-related variables. Associations between sE-cadherin and demographic and disease-related variables are found in Table 2. Significant correlations were observed

Table 1. The serum levels of soluble E-cadherin in women with systemic lupus erythematosus (SLE) and in healthy control women.

	Patients, n = 150	Healthy Controls, n = 31
Age range, yrs	25–63	20–75
Age, yrs, mean (SD)	48.7 (12.7), ns	45.8 (11.3)
Serum sE-cadherin (ng/ml), mean (SD)	93.3 (33.6)*	80.6 (18.6)

* $p < 0.05$. ns: not significant.

between sE-cadherin and patient age (r = 0.25, p < 0.01), disease duration (r = 0.24, p < 0.01), SLICC (r = 0.21, p < 0.01), ESR (r = 0.36, p < 0.0001), serum creatinine (r = 0.42, p < 0.0001), GFR (r = –0.53, p < 0.0001), cholesterol (r = 0.37, p < 0.0001), triglycerides (r = 0.36, p < 0.0001), IL-6 (r = 0.31, p < 0.0001), and MMP-3 (r = 0.31, p < 0.0001).

A multiple regression model was performed using sE-cadherin as the dependent variable and patient age, disease duration, SLICC, ESR, s-creatinine, GFR, cholesterol, triglycerides, IL-6, and MMP-3 as independent variables. S-creatinine, patient age, ESR, and triglycerides remained the most important determinants of serum levels of sE-cadherin levels (R^2 = 0.543; Table 3).

Serum levels of MMP-3 in patients with SLE. MMP have been found to be involved in the extracellular cleavage of E-cadherin[29]. To study whether MMP-3 and MMP-9 is involved in E-cadherin shedding in SLE, the serum levels of MMP-3 were detected and associated with sE-cadherin. Increased levels of MMP-3 were found in patients with SLE compared to healthy controls (25.2 ± 23.4 ng/ml vs 10.2 ± 4.4 ng/ml, respectively, p < 0.01). Besides the significant association with sE-cadherin, MMP-3 is also significantly correlated with ESR (r = 0.21, p = 0.009), CRP (r = 0.26, p = 0.001), s-creatinine (r = 0.35, p < 0.0001), triglycerides (r = 0.21, p = 0.01), and IL-6 (r = 0.45, p < 0.0001). In contrast to MMP-3, MMP-9 was downregulated in patients with SLE compared with controls (288.6 ± 15.6 ng/ml vs 732.2 ± 66.1 ng/ml, respectively, p < 0.001). No significant correlation was found between MMP-9 and sE-cadherin in patients with SLE, suggesting that MMP-3 rather than MMP-9 might be involved in ectodomain shedding of E-cadherin.

Table 2. Correlations between serum levels of soluble E-cadherin and disease-related variables in women with systemic lupus erythematosus (SLE).

Correlation	Serum sE-cadherin, ng/ml	
	r	r_s
Age, yrs	0.25[b]	
Disease duration, yrs		0.24[b]
SLICC		0.21[b]
Erythrocyte sedimentation rate, mm/h		0.36[a]
S-creatinine, μmol/l		0.42[a]
Glomerular filtration rate, ml/minute	–0.53[a]	
GFR 50 (< 50 = 1, ≥ 50 = 0)		0.29[a]
Renal involvement ever by SLE (yes = 1, no = 0)		0.18[c]
Cholesterol, mmol/l	0.37[a]	
Low-density lipoprotein, mmol/l	0.19[c]	
Triglycerides, mmol/l		0.36[a]
Interleukin-6, pg/ml		0.31[a]
MMP-3, ng/ml		0.31[a]

All variables were tested with the Kolmogorov-Smirnov normality test. Pearson correlation was used with the variables were normally distributed, otherwise Spearman correlation was used. Only significant variables are shown. [a] p < 0.001; [b] p < 0.01; [c] p < 0.05. DMARD: disease-modifying antirheumatic drugs; GFR: glomerular filtration rate; r: Pearson correlation coefficient; r_s: Spearman correlation coefficient; SLICC: Systemic Lupus International Collaborative Clinics/ACR Damage Index; MMP: matrix metalloproteinase.

Table 3. Multiple stepwise regression analysis of serum levels of soluble E-cadherin (dependent variable) and demographic and disease-related variables (independent variables).

Constant	sE-cadherin in serum, ng/ml –8.937		
	Beta	SE	p
S-creatinine, μmol/l	0.642	0.069	< 0.001
Patient age, yrs	0.544	0.160	0.001
Erythrocyte sedimentation rate, mm/h	0.263	0.094	0.006
Triglycerides, mmol/l	6.53	2.907	0.026
		R^2	0.543

Increased serum levels of sE-cadherin in patients with SLE and renal damage. To further investigate sE-cadherin in the context of renal damage, we divided patients with SLE into different subgroups (s-creatinine above 90 μmol/l or not, GFR above 50 ml/min or not, and SLE renal involvement ever or not; Figure 1). Significantly higher levels of sE-cadherin were found in patients with s-creatinine over 90 μmol/l than in ones with it below 90 μmol/l (p < 0.0001) and healthy controls (p < 0.001, Figure 1A). No difference was found between patients with s-creatinine below 90 μmol/l and healthy controls. Similar differences were also observed when patients were grouped according to GFR and ever having had nephritis (Figures 1B and 1C).

In contrast to serum sE-cadherin, urine sE-cadherin levels were not associated with s-creatinine levels in SLE. No significant difference in urine levels of sE-cadherin was found between the patients with s-creatinine over 90 μmol/l and ones below 90 μmol/l (20.4 ng/ml vs 17.1 ng/ml, respectively). sE-cadherin levels in urine were also similar in SLE subgroups divided according to GFR or renal involvement ever (data not shown). Intriguingly, significantly lower urine sE-cadherin levels were found in patients with 24-h urine protein ≥ 3.5 g than in patients with < 3.5 g (6.7 ng/ml vs 19.6 ng/ml, respectively, p < 0.05). However, only 6 patients had 24-h urine protein ≥ 3.5 g.

DISCUSSION

In our study, we demonstrated that serum levels of sE-cadherin were increased in female patients with SLE compared to healthy women. sE-cadherin correlated positively to creatinine, age, ESR, and triglycerides in patients with SLE.

The ligand to membrane-bound E-cadherin, αEβ7/CD103, was found on human peripheral blood lymphocytes, and elevated αEβ7/CD103 expression was associated with the presence of oral ulcers or serositis in patients with SLE. This finding suggests that increased

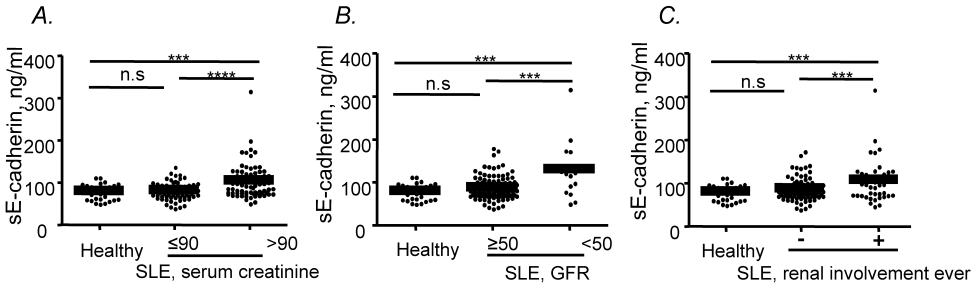

Figure 1. Levels of soluble E-cadherin (sE-cadherin) in the blood of healthy controls and subgroups of patients with systemic lupus erythematosus (SLE) divided according to (A) S-creatinine; (B) calculated GFR; and (C) renal involvement ever by SLE. Bars show the group means. *** $p < 0.001$; **** $p < 0.0001$. n.s: not significant; GFR: glomerular filtration rate.

αEβ7/CD103-E-cadherin interaction might contribute to epithelial inflammation, one of the most common manifestations of SLE[30]. Elevated MMP by stimulation of cytokines and inflammatory mediators in autoimmune diseases[31] are known to cleave membrane-bound E-cadherin and release the sE-cadherin[10]. Therefore, we hypothesized that serum levels of sE-cadherin reflect the disease activity of SLE. The correlations between sE-cadherin and ESR and IL-6 suggest a potential relationship between sE-cadherin release and systemic inflammation in SLE. In accordance with these results, it has been shown that IL-1 causes shedding of E-cadherin from the cell surface of cultured human endothelial cells[32]. In a mouse model, intratracheal antigen or lipopolysaccharide challenge induced focal sE-cadherin release that was correlated with infiltrated neutrophil numbers[33]. Also, elevated serum levels of sE-cadherin have been found in patients with inflammation-related disease such as sepsis[19], inflammatory skin diseases[20], pelvic inflammatory disease[21], and primary Sjögren syndrome[22]. However, we found no significant correlation between sE-cadherin levels and SLEDAI scores. The patients with high disease activity (SLEDAI > 10) in our study had a significantly higher dose of corticosteroid, which may have affected ESR and IL-6 ($p < 0.001$) compared with patients with SLEDAI 1–10. There was also a larger proportion of patients using DMARD, which might also influence the markers of inflammation, in this subgroup of the patients ($p < 0.05$). Additionally, our patient cohort consists of individuals with a large variability in SLE organ involvement. These aspects might contribute to the lack of association between sE-cadherin and SLEDAI.

In contrast to SLEDAI, high SLICC scores were found to be associated with higher levels of sE-cadherin in patients with SLE. Renal damage is one of the most important domains in SLICC. Indeed, higher serum levels of sE-cadherin were found only in patients with elevated s-creatinine, low GFR, and kidney involvement ever by SLE, suggesting a direct association between sE-cadherin levels and renal damage in patients with SLE. One can speculate that elevated sE-cadherin in blood might be the consequence of an accumulating effect due to low GFR, because significantly lower urine sE-cadherin levels were found in patients with 24-h urine protein > 3.5 g compared to patients with 24-h urine protein < 3.5 g. However, that factor does not seem to be the whole explanation, because no significant correlation was found between urine sE-cadherin and serum sE-cadherin. Our question remains: does E-cadherin shedding happen locally in kidneys during renal damage in SLE? In kidneys, E-cadherin is dominantly expressed in tubule epithelia cells, especially in distal and collecting tubules[34,35]. Glomeruli are the target structure of acute inflammation in lupus nephritis, while tubulointerstitial infiltration of inflammatory cells appears frequently and is considered a good indicator of renal function and prognosis[36,37]. In the last decade, the epithelial-to-mesenchymal transition (EMT) of tubule cells has been identified as another significant mechanism, which contributes to progression of tubulointerstitial fibrosis and chronic kidney disease[38]. Importantly, loss of E-cadherin expression is considered a hallmark of EMT. It has been shown that disruption of E-cadherin by MMP directly mediates renal tubular cell EMT and consequently leads to kidney fibrosis[39]. In our study, the relationship between elevated serum levels of MMP-3 and sE-cadherin suggests that MMP-3 might be one of the potent enzyme resources for E-cadherin shedding in SLE. Indeed, serum levels of MMP-3 have been shown to be increased in patients with active lupus nephritis[40]. Thus, our findings suggest a possible connection between MMP-3, sE-cadherin, and renal pathology in SLE nephritis. However, circulating sE-cadherin levels do not necessarily reflect the local E-cadherin expression in kidneys, as transforming growth factor-β1 (an important inducer for E-cadherin shedding) does in SLE[28]. To elucidate the role of E-cadherin shedding in SLE nephritis, we need to further study the expression of E-cadherin and its regulatory factors in kidneys of patients

with active lupus nephritis and those with chronic renal damage.

Patients with SLE have a high risk of cardiovascular diseases (CVD), which connected to the dyslipoproteinemia with high triglycerides (TG)/low high-density lipoprotein in SLE, correlated with disease activity[41]. CVD has become a major cause of mortality in patients with SLE[42]. Interestingly, the death rate among patients with SLE has drastically declined in the past decades, probably as a result of better and earlier treatment, while the risk of cardiovascular death remains unchanged[43]. In our study, besides creatinine, ESR, and age of the patients, TG were positively connected with sE-cadherin. It has been shown before that serum levels of sE-cadherin positively correlate to the age of the patients with gastric cancer[44]. However, the correlation between TG and sE-cadherin was, to our best knowledge, not known before, and it persisted in the multiple regression model. The mechanism for how E-cadherin shedding connects to lipid metabolism in SLE and the clinical significance of this result need to be further investigated.

The clinical implications of our findings are that sE-cadherin was only increased in the patients with pathologically elevated creatinine and low GFR. In the patients with SLE whose kidneys are affected, the sE-cadherin levels were also significantly increased compared with other patients with SLE and healthy controls. The strong correlation between TG and sE-cadherin suggests that sE-cadherin might be an indicator for cardiovascular risk/damage in SLE. All together, increased sE-cadherin levels seem to relate to several domains of disease damage in SLE.

We found elevated serum levels of sE-cadherin in patients with SLE compared with healthy individuals. sE-cadherin was associated with age, TG, s-creatinine, and ESR. To our knowledge, our results showed for the first time a possible relationship between lipid metabolism and E-cadherin shedding in patients with SLE. Importantly, elevated levels of sE-cadherin were only found in patients with SLE and severe renal damage. Our study suggests that sE-cadherin may be used as a biomarker for kidney damage in patients with SLE.

REFERENCES

1. van Roy F, Berx G. The cell-cell adhesion molecule E-cadherin. Cell Mol Life Sci 2008;65:3756-88.
2. Van den Bossche J, Malissen B, Mantovani A, De Baetselier P, Van Ginderachter JA. Regulation and function of the E-cadherin/catenin complex in cells of the monocyte-macrophage lineage and DCs. Blood 2012;119:1623-33.
3. Van den Bossche J, Van Ginderachter JA. E-cadherin: from epithelial glue to immunological regulator. Eur J Immunol 2012;43:34-7.
4. Kubo A, Nagao K, Yokouchi M, Sasaki H, Amagai M. External antigen uptake by Langerhans cells with reorganization of epidermal tight junction barriers. J Exp Med 2009;206:2937-46.
5. Jakob T, Udey MC. Regulation of E-cadherin-mediated adhesion in Langerhans cell-like dendritic cells by inflammatory mediators that mobilize Langerhans cells in vivo. J Immunol 1998;160:4067-73.
6. Jiang A, Bloom O, Ono S, Cui W, Unternaehrer J, Jiang S, et al. Disruption of E-cadherin-mediated adhesion induces a functionally distinct pathway of dendritic cell maturation. Immunity 2007;27:610-24.
7. Manicassamy S, Reizis B, Ravindran R, Nakaya H, Salazar-Gonzalez RM, Wang YC, et al. Activation of beta-catenin in dendritic cells regulates immunity versus tolerance in the intestine. Science 2010;329:849-53.
8. Siddiqui KR, Laffont S, Powrie F. E-cadherin marks a subset of inflammatory dendritic cells that promote T cell-mediated colitis. Immunity 2010;32:557-67.
9. Van den Bossche J, Bogaert P, van Hengel J, Guerin CJ, Berx G, Movahedi K, et al. Alternatively activated macrophages engage in homotypic and heterotypic interactions through IL-4 and polyamine-induced E-cadherin/catenin complexes. Blood 2009;114:4664-74.
10. De Wever O, Derycke L, Hendrix A, De Meerleer G, Godeau F, Depypere H, et al. Soluble cadherins as cancer biomarkers. Clin Exp Metastasis 2007;24:685-97.
11. Gofuku J, Shiozaki H, Doki Y, Inoue M, Hirao M, Fukuchi N, et al. Characterization of soluble E-cadherin as a disease marker in gastric cancer patients. Br J Cancer 1998;78:1095-101.
12. Chan AO, Chu KM, Lam SK, Wong BC, Kwok KF, Law S, et al. Soluble E-cadherin is an independent pretherapeutic factor for long-term survival in gastric cancer. J Clin Oncol 2003;21:2288-93.
13. Matsumoto K, Shariat SF, Casella R, Wheeler TM, Slawin KM, Lerner SP. Preoperative plasma soluble E-cadherin predicts metastases to lymph nodes and prognosis in patients undergoing radical cystectomy. J Urol 2003;170:2248-52.
14. Kuefer R, Hofer MD, Zorn CS, Engel O, Volkmer BG, Juarez-Brito MA, et al. Assessment of a fragment of e-cadherin as a serum biomarker with predictive value for prostate cancer. Br J Cancer 2005;92:2018-23.
15. Gadducci A, Ferdeghini M, Cosio S, Annicchiarico C, Ciampi B, Bianchi R, et al. Preoperative serum E-cadherin assay in patients with ovarian carcinoma. Anticancer Res 1999;19:769-72.
16. Velikova G, Banks RE, Gearing A, Hemingway I, Forbes MA, Preston SR, et al. Serum concentrations of soluble adhesion molecules in patients with colorectal cancer. Br J Cancer 1998;77:1857-63.
17. Shirahama S, Furukawa F, Wakita H, Takigawa M. E- and P-cadherin expression in tumor tissues and soluble E-cadherin levels in sera of patients with skin cancer. J Dermatol Sci 1996;13:30-6.
18. Charalabopoulos K, Gogali A, Dalavaga Y, Daskalopoulos G, Vassiliou M, Bablekos G, et al. The clinical significance of soluble E-cadherin in nonsmall cell lung cancer. Exp Oncol 2006;28:83-5.
19. Pittard AJ, Banks RE, Galley HF, Webster NR. Soluble E-cadherin concentrations in patients with systemic inflammatory response syndrome and multiorgan dysfunction syndrome. Br J Anaesth 1996;76:629-31.
20. Matsuyoshi N, Tanaka T, Toda K, Okamoto H, Furukawa F, Imamura S. Soluble E-cadherin: a novel cutaneous disease marker. Br J Dermatol 1995;132:745-9.
21. Tsai HT, Lee TH, Yang SF, Lin LY, Tee YT, Wang PH. Markedly elevated soluble E-cadherin in plasma of patient with pelvic inflammatory disease. Fertil Steril 2013;99:490-5.
22. Jonsson MV, Salomonsson S, Oijordsbakken G, Skarstein K. Elevated serum levels of soluble E-cadherin in patients with primary Sjogren's syndrome. Scand J Immunol 2005;62:552-9.
23. Almehed K, Forsblad d'Elia H, Kvist G, Ohlsson C, Carlsten H. Prevalence and risk factors of osteoporosis in female SLE patients-extended report. Rheumatology 2007;46:1185-90.

24. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
25. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35:630-40.
26. Gladman DD, Urowitz MB, Goldsmith CH, Fortin P, Ginzler E, Gordon C, et al. The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. Arthritis Rheum 1997;40:809-13.
27. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
28. Jin T, Almehed K, Carlsten H, Forsblad-d'Elia H. Decreased serum levels of TGF-beta1 are associated with renal damage in female patients with systemic lupus erythematosus. Lupus 2012;21:310-8.
29. Noe V, Fingleton B, Jacobs K, Crawford HC, Vermeulen S, Steelant W, et al. Release of an invasion promoter E-cadherin fragment by matrilysin and stromelysin-1. J Cell Sci 2001;114:111-8.
30. Pang M, Abe T, Fujihara T, Mori S, Tsuzaka K, Amano K, et al. Up-regulation of alphaEbeta7, a novel integrin adhesion molecule, on T cells from systemic lupus erythematosus patients with specific epithelial involvement. Arthritis Rheum 1998;41:1456-63.
31. Goetzl EJ, Banda MJ, Leppert D. Matrix metalloproteinases in immunity. J Immunol 1996;156:1-4.
32. Newman W, Beall LD, Carson CW, Hunder GG, Graben N, Randhawa ZI, et al. Soluble E-selectin is found in supernatants of activated endothelial cells and is elevated in the serum of patients with septic shock. J Immunol 1993;150:644-54.
33. Evans SM, Blyth DI, Wong T, Sanjar S, West MR. Decreased distribution of lung epithelial junction proteins after intratracheal antigen or lipopolysaccharide challenge: correlation with neutrophil influx and levels of BALF sE-cadherin. Am J Respir Cell Mol Biol 2002;27:446-54.
34. Baer PC, Bereiter-Hahn J, Schubert R, Geiger H. Differentiation status of human renal proximal and distal tubular epithelial cells in vitro: Differential expression of characteristic markers. Cells Tissues Organs 2006;184:16-22.
35. Nakopoulou L, Lazaris A, Boletis IN, Michail S, Giannopoulou I, Zeis PM, et al. Evaluation of E-cadherin/catenin complex in primary and secondary glomerulonephritis. Am J Kidney Dis 2002;39:469-74.
36. Alexopoulos E, Seron D, Hartley RB, Cameron JS. Lupus nephritis: correlation of interstitial cells with glomerular function. Kidney Int 1990;37:100-9.
37. Giannakakis K, Faraggiana T. Histopathology of lupus nephritis. Clin Rev Allergy Immunol 2011;40:170-80.
38. Liu Y. Epithelial to mesenchymal transition in renal fibrogenesis: pathologic significance, molecular mechanism, and therapeutic intervention. J Am Soc Nephrol 2004;15:1-12.
39. Zheng G, Lyons JG, Tan TK, Wang Y, Hsu TT, Min D, et al. Disruption of E-cadherin by matrix metalloproteinase directly mediates epithelial-mesenchymal transition downstream of transforming growth factor-beta1 in renal tubular epithelial cells. Am J Pathol 2009;175:580-91.
40. Kotajima L, Aotsuka S, Fujimani M, Okawa-Takatsuji M, Kinoshita M, Sumiya M, et al. Increased levels of matrix metalloproteinase-3 in sera from patients with active lupus nephritis. Clin Exp Rheumatol 1998;16:409-15.
41. Svenungsson E, Gunnarsson I, Fei GZ, Lundberg IE, Klareskog L, Frostegard J. Elevated triglycerides and low levels of high-density lipoprotein as markers of disease activity in association with up-regulation of the tumor necrosis factor alpha/tumor necrosis factor receptor system in systemic lupus erythematosus. Arthritis Rheum 2003;48:2533-40.
42. Bjornadal L, Yin L, Granath F, Klareskog L, Ekbom A. Cardiovascular disease a hazard despite improved prognosis in patients with systemic lupus erythematosus: results from a Swedish population based study 1964-95. J Rheumatol 2004;31:713-9.
43. Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum 2006;54:2550-7.
44. Pedrazzani C, Caruso S, Corso G, Marrelli D, Neri A, Berardi A, et al. Influence of age on soluble E-cadherin serum levels prevents its utility as a disease marker in gastric cancer patients. Scand J Gastroenterol 2008;43:765-6.