Circulating Surfactant Protein D Is Decreased in Systemic Lupus Erythematosus

SILJE VERMEDAL HOEGH, ANNE VOSS, GRITH LYKKE SORENSEN, ANETTE HØJ, CHRISTIAN BENDIXEN, PETER JUNKER, and UFFE HOLMSKOV

ABSTRACT. ***Objective.*** Deficiencies of innate immune molecules like mannan binding lectin (MBL) have been implicated in the pathogenesis of systemic lupus erythematosus (SLE). Surfactant protein D (SP-D) and MBL belong to the same family of innate immune molecules — the collectins, which share important structural and functional properties. We aimed to compare concentrations of serum SP-D in patients with SLE and in healthy controls, and to investigate if SP-D is associated with selected disease indicators. We investigated the possible association of the Met11Thr polymorphism with disease, since this polymorphism is an important determinant for serum level, oligomerization pattern, and function of SP-D.

Methods. Serum SP-D was measured using a 5-layer ELISA in 70 SLE patients and 1476 healthy subjects. DNA was genotyped for the Met11Thr variant.

Results. Median SP-D level in serum was 911 ng/ml (95% CI 776–1118) in patients and 1068 ng/ml (95% CI 901–1246) in controls (p = 0.0004). Circulating SP-D did not differ significantly in patients with high, intermediate, or low SLE disease activity. Similarly, SP-D did not correlate with C-reactive protein, erythrocyte sedimentation rate, and anti-dsDNA seropositivity. Genetic analysis did not support an association of the Met11Thr genotype with SLE.

Conclusion. These findings suggest that low SP-D, unrelated to conventional disease indicators, represents an aspect of SLE etiopathogenesis. (First Release Oct 15 2009; J Rheumatol 2009; 36:2449–53; doi:10.3899/jrheum.090069)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS — COLLECTINS
INNATE IMMUNITY — SURFACTANT PROTEIN D

Systemic lupus erythematosus (SLE) is an autoimmune disorder with a broad range of clinical presentations. Its etiology is unknown, but both genetic and environmental factors are implicated[1]. The collectins, including surfactant protein D (SP-D) and mannan binding lectin (MBL), are pattern-recognition molecules of the innate immune system that recognize a variety of ligands, including oligosaccharide structures expressed by bacteria, viruses, and fungi[2]. Collectins are composed of structurally similar oligomers that contain an N-terminal collagenous tail and a C-terminal globular head group with lectin (carbohydrate-binding) activity[3]. C1q, the first member of the classical complement cascade, is related to the collectins by structure and function, except that its globular head lacks lectin activity[3]. Deficiency of C1q and MBL is associated with an increased risk for SLE or a poor prognosis[4-8], and it has been speculated that defects in the clearance of apoptotic material (waste-disposal hypothesis) by early classical complement pathway components as well as other opsonins such as C-reactive protein (CRP) and serum amyloid protein are implicated in the pathophysiology of SLE[9].

Upon binding oligosaccharide structures on bacteria, viruses, and fungi, SP-D mediates aggregation, phagocytosis, and inflammatory effects[10]. SP-D also plays a role in modulating the immune response by inhibiting T lymphocyte proliferation and interleukin 2 production[11], and by inhibiting lipopolysaccharide-elicited inflammatory responses in macrophages[12]. SP-D-deficient mice show increased lung inflammation, increased oxidant production, and decreased macrophage phagocytosis after bacterial lung infection[13]. Gardai, *et al*[14] provided a model for the appar-

From the Medical Biotechnology Center, Institute of Medical Biology, University of Southern Denmark, Odense; Department of Rheumatology C, Odense University Hospital, Odense; and Department of Animal Breeding and Genetics, Danish Institute of Agricultural Sciences, Tjele, Denmark.

Supported by grants from the Danish Rheumatism Association, The A.P. Møller Foundation for the Advancement of Medical Science, Ingemann O. Bucks Foundation, Gårdejer af Stenløse Peder Laurits Petersens Legat, and Guldsmed A.L. & D. Rasmussens Mindefond.

S.V. Hoegh, MSc, PhD student, Medical Biotechnology Center, Institute of Medical Biology; A. Voss, MD, PhD, Associate Professor, Department of Rheumatology C, Odense University Hospital; G.L. Sorensen, MSc, PhD, Associate Professor, Medical Biotechnology Center, Institute of Medical Biology; A. Høj, MSc, PhD, Senior Researcher; C. Bendixen, MSc, PhD, Professor, Department of Animal Breeding and Genetics, Danish Institute of Agricultural Sciences; P. Junker, MD, DMSc, Professor, Department of Rheumatology C, Odense University Hospital; U. Holmskov, MD, PhD, DMSc, Professor, Medical Biotechnology Center, Institute of Medical Biology, University of Southern Denmark.

Address correspondence to Prof. U. Holmskov, Medical Biotechnology Center, Winsløwparken 25, 5000 Odense C, Denmark.
E-mail: uholmskov@health.sdu.dk

Accepted for publication June 8, 2009.

ent paradox that SP-D both enhances and inhibits inflammation. They suggested that SP-D occupied by microbial ligands initiates proinflammatory activity by specific cellular interaction, while free SP-D initiates inhibition of cellular inflammation. In addition to recognizing pathogens, SP-D is also capable of binding to self-derived ligands in the form of apoptotic cells, and thereby facilitating their removal[15].

Like MBL, the serum concentration of SP-D is strongly influenced by genetic factors[16]. Thus, the Met11Thr polymorphism in the N-terminal part of the protein plays an important role in determining the serum level of SP-D by an unknown mechanism. In addition, this polymorphism is an important determinant for the oligomerization pattern and function of the protein[17].

Based on the structural and functional similarities between MBL and SP-D and the association between low MBL and increased risk or a poor prognosis in SLE, our aim was to investigate a possible relationship between SLE and SP-D including disease manifestations and activity. In addition, we studied the distribution of SP-D Met11Thr genotypes in SLE.

MATERIALS AND METHODS

Patients and controls. A random sample of 70 patients classified as having SLE according to the revised American College of Rheumatology (ACR) criteria[18,19] were recruited from a Danish SLE population[20]. Median disease damage was scored according to the Systemic Lupus International Collaborating Clinics/ACR Disease Damage Index (SLICC/ACR DI)[21,22]. Disease activity was scored according to the SLE Disease Activity Index (SLEDAI) score[23]. CRP and erythrocyte sedimentation rate (ESR) were measured by standard laboratory techniques, and anti-dsDNA was quantified by ELISA (Dako, Glostrup, Denmark).

A group of 1476 healthy Danish twin individuals 18–67 years old matched for age, sex, and smoking status served as controls[24]. In total, 425 twins from this group were included for genotyping.

The study was conducted in accord with the Declaration of Helsinki, and signed informed consent was obtained from each patient. The local ethics committee approved the project (J. No. 19940131).

Measurement of SP-D. SP-D in serum was assayed using a 5-layer ELISA as described[25]. Microtiter plates were coated with $F(ab')_2$ anti-human SP-D (K477) at 1 µg/ml in 0.05 M sodium carbonate buffer, pH 9.6. After overnight incubation at 4°C the plates were washed and left in washing buffer (TBS, 0.05% Tween 20, 5 mM $CaCl_2$) for at least 15 min at room temperature. Calibrator, control samples, and samples diluted as appropriate (1:10 to 1:60) in washing buffer were added and incubated overnight at 4°C. This was followed by successive incubations with biotinylated monoclonal anti-human SP-D antibody (Hyb 246-4), horseradish peroxidase-conjugated streptavidin, and o-phenylenediamine in citrate-phosphate buffer, pH 5, containing 0.014% H_2O_2. Adding H_2SO_4 stopped the color reaction. Plates were read at 492 nm in a multichannel spectrophotometer.

Single-nucleotide polymorphism (SNP) analysis. Genomic DNA was extracted from EDTA-treated blood samples using the Maxwell 16 DNA Purification Kit and the Maxwell 16 instrument (Promega, Madison, WI, USA) according to the manufacturer's instructions. Primers and probes for the nonsynonymous thymine (T) to cytosine (C) substitution in position 92 in exon 1 of the *SFTPD* gene resulting in the Met11Thr variant were designed as described (Assay-by-design; Applied Biosystems, Foster City, CA, USA)[16]. The 5 µl reactions contained 1 × Taqman Universal Master Mix, No AmpErase UNG (Applied Biosystems), a 900 nM concentration of both the forward and reverse primer, and a 200 nM concentration of the 2 probes added to dry DNA (25–75 ng) in 384-well optical plates sealed with optical covers. The primer/probe combination was designed to work at one universal set of thermal cycler conditions: 50°C for 2 min, 95°C for 10 min, followed by 40 cycles at 95°C for 15 s and 60°C for 60 s. Thermal cyclers used for this reaction were GeneAmp PCR System 9700 (Applied Biosystems) with 384-well thermal blocks. After thermal cycling, the plates were stored at 4°C (never > 48 h) until they could be read by the fluorescent reader. Fluorescent signals were detected in an Abi-Prism 7900HT sequence detection system (Applied Biosystems). Results were collected and analyzed by Abi-Prism SDS 2.1 software for allelic discrimination.

Statistical analysis. Statistical analyses were performed using Intercooled Stata version 8.2 (www.stata.com). The effects of age, sex, current smoking, and Met11/Thr11 genotype on the SP-D serum level were analyzed using multiple regression analysis in the healthy twin population (1476 individuals) with inclusion of the confounders and 2-way interactions. This regression model was used to predict the SP-D values in healthy individuals that were matched to patients according to the parameters given. To approximate a normal distribution, the SP-D was logarithmically transformed when used as continuous dependent variable in linear regression analysis. Residuals resulting from the linear regression were normally distributed. The equality of matched pairs was tested by the sign test.

Relationships between serum SP-D and disease activity markers were analyzed by multiple linear and logistic regression with inclusion of the confounders age, sex, smoking status, and Met11Thr genotype. Logarithmically transformed SP-D values were used in the analysis. SP-D levels in 2 or 3 groups were compared by Mann-Whitney 2-sample test or Kruskal-Wallis equality of populations rank test, respectively.

Met11Thr genotype and allele frequencies were calculated for patients (n = 70) and controls (n = 425) by means of 2 × 2 and 2 × 3 contingency tables. The twin database was used as the control population, but only one individual in each twin pair was included in the analysis. The observed genotype frequencies were tested for Hardy-Weinberg equilibrium by chi-square analysis. Comparisons of SP-D Met11Thr genotype frequencies in patients and controls were by Fisher's exact test. P values ≤ 0.05 were considered statistically significant.

RESULTS

Patient characteristics are presented in Table 1. SLE patients had significantly lower serum SP-D levels compared with healthy controls matched to each patient for age, sex, smoking status, and Met11Thr genotype (p = 0.0004). Median

Table 1. Characteristics of SLE patients (n = 70).

Characteristic	
Sex (female/male)	66/4
Age, yrs, mean (range)	45 (22–79)
Smoker/nonsmoker	33/37
Disease duration, yrs, mean (range)	16 (1–43)
ACR criteria fulfilled, median (range)	6 (4–10)
Drug treatment, no. (%) patients treated	
Prednisolone	20 (29)
Immunosuppressants (azathioprine and cyclophosphamide)	9 (13)
Disease activity and damage scores, median (range)	
SLEDAI	2 (0–8)
SLICC/ACR DI	2 (0–9)

SLICC/ACR DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Disease Damage Index; SLEDAI: SLE Disease Activity Index.

serum SP-D level was 911 ng/ml (95% CI 776–1118) in patients and 1068 ng/ml (95% CI 901–1246) in controls.

Table 2 shows the partial regression coefficients between disease indicators and serum SP-D. We found no association between serum SP-D and CRP, ESR, anti-dsDNA titer, or SLICC or SLEDAI scores. Stratification of the patients into 3 groups with low (SLEDAI 0–2; n = 50), intermediate (SLEDAI 3–4; n = 11), and high disease activity (SLEDAI > 4; n = 9) revealed median SP-D levels of 949 ng/ml (95% CI 781–1159), 699 ng/ml (95% CI 358–1178), and 901 ng/ml (95% CI 643–1455), respectively (p = 0.35). About half the patients had a history of renal disease (n = 33). SP-D levels in these patients and in the patients without renal disease were 921 ng/ml (95% CI 709–1154) and 901 ng/ml (95% CI 701–1204), respectively (p = 0.86).

In addition, we found no significant differences in serum SP-D stratifying patients according to current/previous and no joint, skin, or lung manifestations (data not shown).

Hardy-Weinberg equilibrium was found in both patients and controls with respect to the Met11Thr polymorphism (data not shown). Thirty-two of the 70 patients (45.7%) carried the Met11/Met11 genotype, 30 (42.9%) the Met11/Thr11 genotype, and 8 (11.4%) the Thr11/Thr11 genotype (Table 3). This overall distribution did not differ significantly between SLE patients and healthy controls (p = 0.20).

Table 2. Relationship between selected disease indicators and serum SP-D. Multiple linear and logistic regression models the mean of the response variable Y as a function of the covariates, where Y = (CRP, ESR, dsDNA, SLICC or SLEDAI) and the covariates are lnSP-D, age, sex, smoking, and Met11Thr polymorphism. The coefficient shown is the estimated regression coefficient for lnSP-D. Anti-dsDNA titer was considered to be positive when > 35 IU/ml.

Response Variable Y	Partial Regression Coefficient $ß_{lnSP\text{-}D}$ (95% CI)	p
CRP, mg/ml	–4.42 (–17.35; 8.52)	0.48
ESR, mm/h	–7.18 (–21.39; 7.03)	0.31
Anti-dsDNA (pos/neg)	0.55 (–0.33; 1.44)	0.22
SLICC	–0.53 (–1.56; 0.49)	0.30
SLEDAI	0.34 (–0.55; 1.23)	0.45

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SLICC: Systemic Lupus International Collaborating Clinics; SLEDAI: SLE Disease Activity Index.

When SLE patients were stratified according to Met11Thr genotype, a trend was observed toward decreasing SP-D from Met11/Met11 to the Thr11/Thr11 genotype: 1046 ng/ml (95% CI 810–1206) versus 784 ng/ml (95% CI 589–1124) versus 552 ng/ml (95% CI 303–1541) in the Met11/Met11, Met11/Thr11, and Thr11/Thr11 genotype groups, respectively (p = 0.16).

DISCUSSION

In this first study on SP-D in SLE, we found that SP-D in serum was significantly decreased by approximately 15% compared with carefully matched healthy control subjects. Of note, however, no relationship was found between SP-D and clinical phenotype and a selection of disease indicators including CRP, ESR, anti-dsDNA, and SLEDAI and SLICC scores. There was no significant difference in frequencies of Met11Thr genotype between the patient and control groups.

The predicted healthy control levels of SP-D were based on a multiple regression model that included the confounders age, sex, current smoking, and the Met11/Thr11 genotype, implying that the model predicted serum SP-D levels in matched controls with the same age, sex, smoking status, and Met11Thr genotype as each individual patient with SLE.

Serum SP-D partly reflects pulmonary leakage, and in patients with a range of different lung diseases serum SP-D has been reported to be elevated compared to the healthy control level (as reviewed[26,27]). By contrast, we previously reported that SP-D is initially decreased on the day of admission to hospital in patients with acute bacterial pneumonia. Following antibiotic treatment SP-D levels increased steeply, reaching peak levels at day 5 after admission[25]. Similarly, we recently observed that serum SP-D is decreased in patients with newly diagnosed and untreated rheumatoid arthritis. During 1-year followup the patients improved significantly in all measures of disease activity, and in the same period serum SP-D increased significantly and almost reached the level of the healthy matched controls[28]. In the present study on SLE, we show for the first time that SP-D is also decreased in this chronic autoimmune disease. There was no association with conventional disease activity measures in either disease, indicating that SP-D in serum reflects a distinctive aspect of the disease pathogenesis undetected by currently available disease markers.

Table 3. Distribution of SP-D Met11Thr genotype frequencies and corresponding serum SP-D levels.

Genotype	SLE Patients, n (%)	Controls, n (%)	p	SP-D, ng/ml (95% CI)*
Met11/Met11	32 (45.7)	152 (35.8)	0.20	1046 (810–1206)
Met11/Thr11	30 (42.9)	196 (46.1)		784 (589–1124)
Thr11/Thr11	8 (11.4)	77 (18.1)		522 (303–1541)
Total	70 (100.0)	425 (100)		

* Median SP-D values in SLE patients divided into SP-D Met11Thr genotypes. SP-D genotype frequencies were compared by Fisher's exact test.

These observations in inflammatory conditions with different etiologies indicate that serum SP-D may be affected by an ongoing infection or a chronic inflammatory state within or outside the lung, and is not solely dependent on the permeability of pulmonary lung vessels. The exact mechanism for the low SP-D in SLE is not known.

Virtually all C1q-deficient humans develop SLE[29]. Because C1q binds to blebs generated in apoptotic cells[30], it has been speculated that impaired clearance of these autoantigens may be important in the pathogenesis of SLE. Like C1q, SP-D binds to apoptotic cells as well as genomic DNA[31], and SP-D facilitates the clearance of DNA[32] and apoptotic cells[33]. Mice deficient in SP-D develop heavy lung infiltrations of inflammatory cells and exhibit increased numbers of dying cells in bronchoalveolar lavage[34]. These observations suggest that SP-D plays a critical role in removal of cellular waste. Thus, defective clearance of apoptotic material due to low SP-D could result in prolonged exposure of autoantigens to the immune system, thereby triggering an immune response to nuclear antigens.

A large proportion of the patients with SLE were treated with glucocorticosteroids, mainly in low dose (≤ 7.5 mg/day). However, since glucocorticoids enhance SP-D expression *in vitro*[35] and *in vivo*[36], they would tend to decrease the difference between SLE and healthy subjects. Consequently, it would be anticipated that SP-D would be decreased even more in steroid-naive patients. Analysis of sera from steroid-naive patients is needed in order to investigate this issue in detail.

When SP-D levels were compared in SLE subsets with different disease activity, we found no significant differences, indicating that low SP-D in SLE is not primarily due to differences in drug therapy, since patients with high SLEDAI score were generally on more intense immunosuppressive treatment than the SLE patients with low disease activity. Finally, low SP-D did not appear to result from increased renal loss, since SP-D did not differ between patients with and without a history of renal disease.

Serum SP-D in healthy individuals is highly variable and strongly determined by genetic factors, with a heritability coefficient of $h^2 = 0.83$. The Met11Thr polymorphism, which results in an amino acid substitution from methionine to threonine at position 11 in the mature protein, explains nearly half of the heritability[16]. In accord with this, we also observed decreasing serum SP-D levels in SLE patients with Met11/Met11, Met11/Thr11, and Thr11/Thr11 genotype; however, this did not reach statistical significance.

Clinical studies have associated the Met11Thr variation with disease. Thus, the Met11 allele was associated with severe respiratory syncytial virus infection in infants[37], and the Thr11 allele was associated with increased susceptibility to tuberculosis[38]. In addition, a haplotype containing the Met11 allelic variant was protective against development of respiratory distress syndrome[39]. Our results do not support a significant association of this polymorphism with SLE.

One major limitation of our study is the relatively small sample size, which reduced the statistical power. In addition, only a small proportion of subjects had active disease. However, subgroup comparisons including patients with low, intermediate, and high disease activity and different clinical manifestations did reveal differences with respect to SP-D in the circulation.

We report for the first time that serum SP-D concentration is subnormal in patients with SLE, and that this decrease is unrelated to disease activity, damage, clinical phenotype, and conventional serum markers, indicating that low SP-D represents an aspect of the etiopathogenesis of SLE that is not reflected by conventional disease markers.

ACKNOWLEDGMENT

Thanks to Kirsten Junker for skilled technical assistance. We also thank investigators of the twin study of the metabolic syndrome and related components (GEMINAKAR) for providing serum and DNA samples.

REFERENCES

1. Mok CC, Lau CS. Pathogenesis of systemic lupus erythematosus. J Clin Pathol 2003;56:481-90.
2. Holmskov U, Thiel S, Jensenius JC. Collections and ficolins: Humoral lectins of the innate immune defense. Annu Rev Immunol 2003;21:547-78.
3. Wright JR. Immunoregulatory functions of surfactant proteins. Nat Rev Immunol 2005;5:58-68.
4. Manderson AP, Botto M, Walport MJ. The role of complement in the development of systemic lupus erythematosus. Annu Rev Immunol 2004;22:431-56.
5. Garred P, Voss A, Madsen HO, Junker P. Association of mannose-binding lectin gene variation with disease severity and infections in a population-based cohort of systemic lupus erythematosus patients. Genes Immun 2001;2:442-50.
6. Lee YH, Witte T, Momot T, Schmidt RE, Kaufman KM, Harley JB, et al. The mannose-binding lectin gene polymorphisms and systemic lupus erythematosus: Two case-control studies and a meta-analysis. Arthritis Rheum 2005;52:3966-74.
7. Ip WK, Chan SY, Lau CS, Lau YL. Association of systemic lupus erythematosus with promoter polymorphisms of the mannose-binding lectin gene. Arthritis Rheum 1998;41:1663-8.
8. Sullivan KE, Wooten C, Goldman D, Petri M. Mannose-binding protein genetic polymorphisms in black patients with systemic lupus erythematosus. Arthritis Rheum 1996;39:2046-51.
9. Walport MJ. Complement. Second of two parts. N Engl J Med 2001;344:1140-4.
10. Crouch EC. Surfactant protein-D and pulmonary host defense. Respir Res 2000;1:93-108.
11. Borron PJ, Crouch EC, Lewis JF, Wright JR, Possmayer F, Fraher LJ. Recombinant rat surfactant-associated protein D inhibits human T lymphocyte proliferation and IL-2 production. J Immunol 1998;161:4599-603.
12. Yamazoe M, Nishitani C, Takahashi M, Katoh T, Ariki S, Shimizu T, et al. Pulmonary surfactant protein D inhibits lipopolysaccharide (LPS)-induced inflammatory cell responses by altering LPS binding to its receptors. J Biol Chem 2008;283:35878-88.
13. LeVine AM, Whitsett JA, Gwozdz JA, Richardson TR, Fisher JH, Burhans MS, et al. Distinct effects of surfactant protein A or D deficiency during bacterial infection on the lung. J Immunol

2000;165:3934-40.
14. Gardai SJ, Xiao YQ, Dickinson M, Nick JA, Voelker DR, Greene KE, et al. By binding SIRP-alpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. Cell 2003;115:13-23.
15. Vandivier RW, Ogden CA, Fadok VA, Hoffmann PR, Brown KK, Botto M, et al. Role of surfactant proteins A, D, and C1q in the clearance of apoptotic cells in vivo and in vitro: Calreticulin and CD91 as a common collectin receptor complex. J Immunol 2002;169:3978-86.
16. Sorensen GL, Hjelmborg JB, Kyvik KO, Fenger M, Hoj A, Bendixen C, et al. Genetic and environmental influences of surfactant protein D serum levels. Am J Physiol Lung Cell Mol Physiol 2006;290:L1010-7.
17. Leth-Larsen R, Garred P, Jensenius H, Meschi J, Hartshorn K, Madsen J, et al. A common polymorphism in the SFTPD gene influences assembly, function, and concentration of surfactant protein D. J Immunol 2005;174:1532-8.
18. 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.
19. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
20. Laustrup H, Heegaard NH, Voss A, Green A, Lillevang ST, Junker P. Autoantibodies and self-reported health complaints in relatives of systemic lupus erythematosus patients: A community based approach. Lupus 2004;13:792-9.
21. Gladman DD, Ginzler E, Goldsmith CH, Fortin P, Liang M, Urowitz MB, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363-9.
22. 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.
23. 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.
24. Schousboe K, Visscher PM, Henriksen JE, Hopper JL, Sorensen TI, Kyvik KO. Twin study of genetic and environmental influences on glucose tolerance and indices of insulin sensitivity and secretion. Diabetologia 2003;46:1276-83.
25. Leth-Larsen R, Nordenbaek C, Tornoe I, Moeller V, Schlosser A, Koch C, et al. Surfactant protein D (SP-D) serum levels in patients with community-acquired pneumonia. Clin Immunol 2003;108:29-37.
26. Hartl D, Griese M. Surfactant protein D in human lung diseases. Eur J Clin Invest 2006;36:423-35.
27. Sorensen GL, Husby S, Holmskov U. Surfactant protein A and surfactant protein D variation in pulmonary disease. Immunobiology 2007;212:381-416.
28. Hoegh SV, Lindegaard HM, Sorensen GL, Hoj A, Bendixen C, Junker P, et al. Circulating surfactant protein D is decreased in early rheumatoid arthritis: A 1-year prospective study. Scand J Immunol 2008;67:71-6.
29. Arnett FC, Reveille JD. Genetics of systemic lupus erythematosus. Rheum Dis Clin North Am 1992;18:865-92.
30. Korb LC, Ahearn JM. C1q binds directly and specifically to surface blebs of apoptotic human keratinocytes: Complement deficiency and systemic lupus erythematosus revisited. J Immunol 1997;158:4525-8.
31. Palaniyar N, Clark H, Nadesalingam J, Hawgood S, Reid KB. Surfactant protein D binds genomic DNA and apoptotic cells, and enhances their clearance, in vivo. Ann NY Acad Sci 2003;1010:471-5.
32. Palaniyar N, Clark H, Nadesalingam J, Shih MJ, Hawgood S, Reid KB. Innate immune collectin surfactant protein D enhances the clearance of DNA by macrophages and minimizes anti-DNA antibody generation. J Immunol 2005;174:7352-8.
33. Schagat TL, Wofford JA, Wright JR. Surfactant protein A enhances alveolar macrophage phagocytosis of apoptotic neutrophils. J Immunol 2001;166:2727-33.
34. Clark H, Palaniyar N, Strong P, Edmondson J, Hawgood S, Reid KB. Surfactant protein D reduces alveolar macrophage apoptosis in vivo. J Immunol 2002;169:2892-9.
35. Dulkerian SJ, Gonzales LW, Ning Y, Ballard PL. Regulation of surfactant protein D in human fetal lung. Am J Respir Cell Mol Biol 1996;15:781-6.
36. Wang JY, Yeh TF, Lin YC, Miyamura K, Holmskov U, Reid KB. Measurement of pulmonary status and surfactant protein levels during dexamethasone treatment of neonatal respiratory distress syndrome. Thorax 1996;51:907-13.
37. Lahti M, Lofgren J, Marttila R, Renko M, Klaavuniemi T, Haataja R, et al. Surfactant protein D gene polymorphism associated with severe respiratory syncytial virus infection. Pediatr Res 2002;51:696-9.
38. Floros J, Lin HM, Garcia A, Salazar MA, Guo X, DiAngelo S, et al. Surfactant protein genetic marker alleles identify a subgroup of tuberculosis in a Mexican population. J Infect Dis 2000;182:1473-8.
39. Thomas NJ, Fan R, Diangelo S, Hess JC, Floros J. Haplotypes of the surfactant protein genes A and D as susceptibility factors for the development of respiratory distress syndrome. Acta Paediatr 2007;96:985-9.