Serum complement factor H is associated with clinical and pathological activities of patients with lupus nephritis

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Abstract

Objective. The aim of this study was to investigate serum complement factor H (CFH) and its associations with clinical and pathological features in patients with LN.

Methods. Serum CFH was detected in 241 LN patients, 38 active and 11 inactive patients with SLE without clinical evidence of renal involvement and 51 normal controls. Serum CFH autoantibodies and CFH Tyr402His were screened in the 241 LN patients. CFH deposition in kidneys was detected in some patients.

Results. Serum CFH levels in patients with LN at active phase were significantly lower than in 38 SLE patients or in normal controls. No serum anti-CFH autoantibodies were detected in patients with LN, and there was no significant difference in CFH Tyr402His distribution between patients with LN and normal controls. Glomerular expression of CFH was stronger than in normal controls. Serum CFH levels were mildly negatively associated with SLEDAI scores ($r = -0.204$, $P = 0.001$) and positively associated with serum C3 ($r = 0.367$, $P < 0.001$) and haemoglobin levels ($r = 0.193$, $P = 0.003$). Patients with LN class III, subclass IV-S and those with thrombotic microangiopathy had the lowest serum CFH.

Conclusion. Serum CFH levels were associated with disease activity of LN.

Key words: SLE, lupus nephritis, complement factor H.

Introduction

The pathogenesis of SLE and LN involves autoantibody production, immune complex deposition, aberrant disposal of apoptosis and complement activation [1]. The role of the complement system in SLE is still controversial because it acts as a double-edged sword [2]. To prevent complement-induced host injury and inflammation, strict regulation of complement activation both in circulation and on the cell surface is crucial. One of the key regulators is complement factor H (CFH), the major circulating regulator of the complement alternative pathway.

CFH is an abundant 150-kDa glycoprotein composed of 20 repetitive domains termed short consensus repeats (SCRs). CFH binds to C3b, accelerates decay of the alternative pathway C3-convertase (C3bBb) and acts as a co-factor for the factor I-mediated proteolytic inactivation of C3b. CFH binds to clusters on the surfaces of host cells (but not to bacterial pathogens), and the binding is followed by N-terminal regulatory activity of C3b to protect the host cell from accidental immune damage [3]. Some studies have demonstrated that activation of the alternative complement pathway could accurately reflect disease activity and ongoing activation paralleled with flares in patients with SLE [4–9]. Further studies suggest that a deficiency in components of the alternative pathway, such as CFH, cause susceptibility to SLE [10–12]. Moreover, a recent study has shown that CFH deficiency accelerates the development of LN in lupus-prone mice MRL-lpr [13] and genetic variants in CFH and CFH-related...
genes with SLE susceptibility [14]. Therefore we speculated that serum CFH may be involved in the pathogenesis of SLE, especially LN, and may be used as a useful biomarker.

In our study we detected serum and renal CFH levels in situ, its autoantibodies and genetic background in patients with LN. The associations between serum CFH and clinicopathological characteristics, including renal outcome, were further analysed.

Methods

Patients

Data from 241 patients with renal biopsy-proven LN, diagnosed between January 2000 and August 2008 in Peking University First Hospital, were collected on presentation and during follow-up. Thirty-eight patients with active and 11 with inactive SLE with negative urinalysis (urinary protein excretion <0.5 g/day or <3+ and without any cast, e.g. red cell cast, haemoglobin cast, granular cast or mixed cast) and normal renal function, were selected as disease control. The patients all fulfilled the 1997 ACR revised criteria for SLE [15].

Clinical evaluation

The following clinical data were collected and analysed: gender, fever, anaemia, leucocytopenia, thrombocytopenia, haematuria and leucocyturia. Clinical disease activity was assessed using the SLEDAI [16, 17]. The criteria for active disease and remission of SLE disease activity were based on SLEDAI score: patients with SLEDAI scores >10 were defined as in active phase, whereas patients with scores <4 were defined as in remission phase [17]. We defined the criteria for clinical renal remission as previously reported [18]. Remission of LN included complete remission and partial remission. Complete remission was defined as urinary protein excretion <0.3 g/day, normal urinary sediment [red blood cells (RBC) <5 per high-power field (HP), white blood cells (WBC) <5/HP], normal serum albumin and normal renal function. Partial remission was defined as any one of the following items: decrease in serum creatinine to <130 µmol/l for patients with a baseline serum creatinine level ≥130 µmol/l, but <260 µmol/l; decrease of serum creatinine by >50% for patients with a baseline serum creatinine level >260 µmol/l; decrease in urinary protein excretion by >50% and <3.0 g/day, with a serum albumin level ≥30 g/l and stable renal function.

The patients were followed up in our outpatient clinic specified for LN. The primary end point was defined as death, and secondary end points were defined as end stage renal disease or doubling of serum creatinine.

Laboratory assessment

Serum ANAs, anti-dsDNA antibodies, anti-extractable nuclear antigen antibodies and serum C3 were all detected by commercial kits.

Renal histopathology

The renal biopsy specimens were examined by light microscopy and direct IF. LN was re-classified according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system [19].

Light microscopy examination

Renal biopsy specimens were fixed in 4.5% buffered formaldehyde for light microscopy. Consecutive serial 3-µm sections were used for histological staining. Stains used included haematoxylin and eosin, periodic acid-Schiff, silver methenamine and Masson’s trichrome. Pathological parameters such as activity indices and chronicity indices were determined by renal pathologists using a previously reported system involving semi-quantitative scoring of specific biopsy features with minor modification [20, 21]. The activity indices include endocapillary hypercellularity, cellular crescents, karyorrhexis/fibrinoid necrosis, subendothelial hyaline deposits, interstitial inflammation and leucocyte infiltration, whereas the chronicity indices include glomerular sclerosis, fibrous crescents, tubular atrophy and interstitial fibrosis.

Direct IF examination

The intensity of fluorescence of direct IF for IgG, IgA, IgM, C3, C1q and fibrin deposits was semi-quantitatively graded from 0 to 4.

Detection of CFH deposition in kidney by immunohistochemistry

The method was modified as previously described [22]. Renal tissues obtained from six normal parts of nephrectomized kidneys due to renal carcinoma were used as normal controls. The extent of glomerular staining for CFH was evaluated at 400× magnification and scored semi-quantitatively: 0, no staining; 1, weak and spotty intraglomerular staining; 2, moderate and segmental intraglomerular staining; and 3, strong and diffuse (involving >50% of the glomerular surface area) intraglomerular staining.

Serum and DNA samples

Sera were obtained from peripheral blood on the same day as the renal biopsy before initiation of immunosuppressive treatment. Sera from 51 healthy subjects, matched for gender and age, were used as normal controls. All sera were stored at −70°C until use.

Genomic DNA was isolated from whole blood using a modified salt extraction technique [23]. Three hundred and five geographically and ethnically matched healthy controls were enrolled as normal controls in the present study. The DNA samples were stored at −70°C until use.

Informed consent was obtained for blood and DNA sampling and renal biopsy from each patient. The research was in compliance with the Declaration of Helsinki. The study was approved by the local ethics committees of Peking University First Hospital.
Detection of serum CFH levels using ELISA
The method of detecting serum CFH was the same as previously described [22] with minor modification. The CFH level of each sample was calculated using CurveExpert 1.3 (Hyams Development, http://www.curveexpert.net/). All assays were run in duplicate, and when standard errors were >10%, samples were routinely re-analysed.

Serial concentrations of commercially available highly purified human factor H were used to develop a standard curve. The linear portion of the curve was subsequently used for the measurement of serum factor H.

Detection of serum CFH autoantibodies using ELISA
Serum CFH autoantibodies were detected by ELISA as described previously [24].

Genotyping of a common single nucleotide polymorphism (SNP) of CFH
It has been reported that multiple CFH exonic SNPs are associated with various human diseases. CFH Tyr402His (rs1061170) was the most common non-synonymous SNP of CFH. In our study, genotyping of CFH Tyr402His (rs1061170) was performed using restriction fragment length polymorphism detection technique, as previously described [25].

Statistical analysis
Statistical software SPSS 10.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. Quantitative data were expressed as mean ± s.d., or median with range (minimum–maximum). For comparison of clinical and pathological features of patients, the unpaired t-test was used for comparison of continuous data, one-way analysis of variance was used for the same continuous data in different groups and non-parameter methods were used for categorical data with Bonferroni correction for multiple testings. Kaplan-Meier curves were used to analyse patient outcome. P < 0.05 was considered statistically significant.

Results
Demographic features of patients and controls
The demographic features of patients with LN, SLE without renal involvement and normal controls are shown in Table 1. Gender and age were comparable among the three groups.

Detection range of serum CFH of the sandwich ELISA
Purified human CFH was used to establish a standard curve. The CFH could be detected by the sandwich ELISA at a range of 16.4–1050 µg/ml.

Serum CFH levels in patients and controls
The serum CFH was 561.3 ± 179.7 (274.2–924.8) µg/ml in normal controls. The mean serum CFH level in the LN group was significantly lower than that in active SLE without renal involvement (409.6 ± 192.7 µg/ml vs 705.6 ± 196.5 µg/ml, P = 0.001) and that in normal controls (409.6 ± 192.7 µg/ml vs 561.3 ± 179.7 µg/ml, P = 0.006). The mean serum CFH level in active SLE without renal involvement was significantly higher than that in normal controls (P < 0.001) (Fig. 1A). Serum CFH levels in both active and remission phases from 45 patients with LN (37 patients with complete remission and 8 patients with partial remission) were also examined. The mean serum CFH level of LN in remission was significantly increased compared with that in the active phase (404.5 ± 184.6 µg/ml vs 287.5 ± 146.8 µg/ml, P = 0.001) (Fig. 1B). The mean serum CFH level of inactive non-renal SLE was significantly lower than that in the active phase (468.6 ± 122.1 µg/ml vs 705.6 ± 196.5 µg/ml, P < 0.001). However, there was no significant difference in the mean serum CFH levels between inactive non-renal SLE and normal controls (468.6 ± 122.1 µg/ml vs 561.3 ± 179.7 µg/ml, P = 0.107).

Associations between serum CFH levels and clinical and laboratory parameters in patients with LN
There was no significant difference in serum CFH levels between female and male patients with LN (405.3 ± 194.8 µg/ml vs 432.2 ± 182.1 µg/ml, P = 0.425). There was no association between serum CFH level and age (r = 0.014, P = 0.83).

In clinical data, the serum CFH levels were significantly lower in patients presenting with haematuria (P = 0.006), non-infectious leucocyturia (P = 0.023), anaemia (P = 0.011) and thrombocytopenia (P = 0.036) compared with those without these manifestations in LN. There was a mild inverse association between SLEDAI scores

Table 1 Demographic data and serum CFH levels of patients and controls

<table>
<thead>
<tr>
<th></th>
<th>LN</th>
<th>NR-SLE</th>
<th>Normal control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers of subjects</td>
<td>241</td>
<td>38</td>
<td>51</td>
</tr>
<tr>
<td>Age, mean ± s.d. (range), years</td>
<td>32.9 ± 11.3 (14–70)</td>
<td>32.2 ± 12.3 (8–56)</td>
<td>36.4 ± 7.0 (21–47)</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>37/204</td>
<td>6/32</td>
<td>12/39</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>17.8 ± 5.8</td>
<td>15.2 ± 4.1</td>
<td>0</td>
</tr>
<tr>
<td>Serum CFH, mean ± s.d., µg/ml</td>
<td>409.6 ± 192.7</td>
<td>705.6 ± 196.5</td>
<td>561.3 ± 179.7</td>
</tr>
</tbody>
</table>

NR-SLE: SLE without renal involvement; SLEDAI: SLE Disease Activity Index.
(A) Serum CFH levels in patients with LN, SLE without renal involvement and normal controls. (B) Serum CFH levels in patients with LN in the active and remission phases. (C) Serum CFH levels in patients with different pathological classes and subclasses of LN, based on the 2003 ISN/RPS LN classification.
and serum CFH levels in patients with LN ($r = -0.204$, $P = 0.001$).

In laboratory findings, the serum CFH levels were significantly lower in patients presenting with positive parameters for ANA ($P = 0.043$) and anti-ds-DNA ($P = 0.027$) compared with those without these parameters in LN. There were mild associations between serum CFH levels and serum C3 and haemoglobin levels ($r = 0.367$, $P < 0.001$; $r = 0.193$, $P = 0.003$, respectively) in patients with LN.

All of the $P$-values shown earlier in the text were not corrected for multiple testings. $P < 0.008 (0.05/6)$ after Bonferroni correction was considered statistically significant.

Associations between serum CFH levels and renal histopathological features in patients with LN

Serum CFH levels in different pathological classes of LN are listed in Table 2 and Fig. 1C. There were significant differences in serum CFH levels among various pathological classes (II–V) in patients with LN ($P < 0.001$). The serum CFH level of class III LN was the lowest among the four classes (III vs II, $P = 0.003$; III vs IV, $P = 0.038$; III vs V, $P < 0.001$). The serum CFH level in class IV was also significantly lower than that in class V ($P = 0.001$). The serum CFH level in class III + V was significantly higher than that in class III only ($P = 0.008$). Similarly, the serum CFH level in class IV + V was also significantly higher than that of class V alone ($P = 0.048$). It should be noted that the serum CFH level in IV-S was significantly lower than that in IV-G and the other classes except class III (IV-S vs IV-G, $P = 0.007$; IV-S vs II, $P = 0.002$; IV-S vs V, $P < 0.001$; IV-S vs III, $P = 0.593$). Furthermore, we focused on class IV LN patients combined with thrombotic microangiopathy (TMA) and found that those patients had the lowest serum CFH level ($136.0 \pm 24.0 \mu g/ml$).

Serum CFH levels were mildly negatively associated with renal activity indices scores ($r = -0.17$, $P = 0.008$), endocapillary hypercellularity ($r = -0.198$, $P = 0.002$) and leucocyte infiltration ($r = -0.281$, $P < 0.001$). No association was found in other indices.

**Table 2** Serum CFH levels of patients with different pathological classes and subclasses of LN

<table>
<thead>
<tr>
<th>Class of LN</th>
<th>Subjects (n)</th>
<th>Serum CFH level, mean ± s.d., μg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure II</td>
<td>10</td>
<td>500.7 ± 161.9</td>
</tr>
<tr>
<td>Pure III</td>
<td>22</td>
<td>300.9 ± 98.7</td>
</tr>
<tr>
<td>Pure IV</td>
<td>116</td>
<td>386.0 ± 191.2</td>
</tr>
<tr>
<td>IV-G</td>
<td>100</td>
<td>400.5 ± 192.4</td>
</tr>
<tr>
<td>IV-S</td>
<td>16</td>
<td>295.3 ± 160.1</td>
</tr>
<tr>
<td>Pure V</td>
<td>55</td>
<td>493.5 ± 182.9</td>
</tr>
<tr>
<td>III + V</td>
<td>17</td>
<td>458.9 ± 134.2</td>
</tr>
<tr>
<td>IV + V</td>
<td>17</td>
<td>392.2 ± 222.8</td>
</tr>
<tr>
<td>LN combined TMA(IV)</td>
<td>4</td>
<td>136.0 ± 24.0</td>
</tr>
</tbody>
</table>

TMA: thrombotic angiopathy.

CFH deposition in renal tissues in patients with LN

CFH deposition in renal tissues was investigated in nine patients with LN. CFH was mainly expressed in glomerular capillary loops and mesangia. On the whole, the expression of CFH in patients with LN was more dispersive and stronger than that of normal controls (Fig. 2). The details of serum CFH levels, glomerular CFH deposition intensity, serum C3 levels and glomerular C3 deposition intensity are listed in Table 3. Serum levels of CFH did not parallel glomerular CFH expression. In some patients, the lower the serum levels of CFH, the stronger the glomerular CFH expression. There was no significant association between glomerular CFH expression and the intensity of glomerular deposition of routinely detected complement components (C3 and C1q), immunoglobulins (IgG, IgA and IgM) and fibrin.

Association of serum CFH levels and renal outcome in patients with LN

In our cohort study, patients with LN were followed up for a mean duration of 54.7 ± 54.5 months (6–360 months). We evaluated the association between serum CFH levels and renal survival by Kaplan–Meier survival analysis. It was found that the serum CFH level was not a risk factor for renal outcome in our patients with LN ($P = 0.804$, HR = 1.000, 95% CI 0.998–1.002). Patients were classified into two groups according to whether their serum CFH level was lower or higher than the mean serum CFH level of normal controls. Patients in group 1 had lower serum CFH levels and those in group 2 had higher serum CFH levels. However, there was still no significant difference in renal survival between the two groups ($P = 0.954$). (Details are in supplementary figure, available at Rheumatology Online.)

Detection of serum CFH autoantibodies in patients with LN and controls

Serum autoantibodies against CFH could not be detected in patients with LN and healthy controls by the ELISA technique using purified human CFH as solid phase antigen.

Genotyping of a common CFH Tyr402His (rs1061170) polymorphism in patients with LN

The LN group and normal control group both satisfied Hardy–Weinberg equilibrium. In the LN group, 29/241 (12.0%) had the mutation Tyr for His. In normal controls, 35/305 (11.5%) had the mutation Tyr for His. There was no significant difference between the two groups ($P = 0.894$). No associations were found between the CFH Tyr402His SNP and clinical and pathological features in patients with LN.

Discussion

The role of complement activation in SLE and LN has been assumed for many years. It was reported that deficiency in components of the alternative pathway, such as CFH, cause susceptibility to SLE [10]. Moreover, recent
Fig. 2 Glomerular CFH expression in patients with LN.

(A–C) Paraffin sections for glomerular CFH expression by immunohistochemistry in patients with LN, scored 1–3, respectively. (D) Normal kidney control. (E) Negative control in normal kidney tissue. The primary antibody was replaced by PBS. The expression of CFH is indicated by arrows.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Class of LN</th>
<th>Serum CFH levels at the time of renal biopsy, μg/ml</th>
<th>Intensity of glomerular CFH staining by IHC</th>
<th>Serum C3 levels at the time of renal biopsy, g/l</th>
<th>Intensity of C3 staining by IF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IV</td>
<td>257.4</td>
<td>1+</td>
<td>0.17</td>
<td>2+</td>
</tr>
<tr>
<td>2</td>
<td>IV</td>
<td>273.6</td>
<td>2+</td>
<td>0.52</td>
<td>3+</td>
</tr>
<tr>
<td>3</td>
<td>IV</td>
<td>274.4</td>
<td>1+</td>
<td>0.23</td>
<td>2+</td>
</tr>
<tr>
<td>4</td>
<td>IV</td>
<td>327.4</td>
<td>3+</td>
<td>0.32</td>
<td>2+</td>
</tr>
<tr>
<td>5</td>
<td>IV</td>
<td>449.4</td>
<td>1+</td>
<td>0.56</td>
<td>3+</td>
</tr>
<tr>
<td>6</td>
<td>IV</td>
<td>490.0</td>
<td>3+</td>
<td>0.14</td>
<td>2+</td>
</tr>
<tr>
<td>7</td>
<td>IV</td>
<td>614.8</td>
<td>3+</td>
<td>0.4</td>
<td>4+</td>
</tr>
<tr>
<td>8</td>
<td>IV</td>
<td>694.8</td>
<td>1+</td>
<td>0.19</td>
<td>3+</td>
</tr>
<tr>
<td>9</td>
<td>V</td>
<td>733.4</td>
<td>1+</td>
<td>0.48</td>
<td>2+</td>
</tr>
</tbody>
</table>

IHC: immunohistochemistry.
studies have shown that CFH deficiency accelerates the development of LN in lupus-prone MRL-lpr mice [13] and genetic variants in CFH, and CFH-related genes are associated with SLE susceptibility [14]. However, there is still a lack of studies on serum CFH in patients with LN.

In our study we found that the serum CFH levels in active LN were significantly lower than in SLE without clinical renal involvement or in normal controls. More importantly, the serum CFH levels increased significantly in the remission phase. These data might indicate that serum CFH level is associated with disease activity in LN. The mechanism for the lower serum CFH levels in active LN is still unclear and might be explained by the following reasons: (i) as CFH is a protective regulator in the complement system, it may be related to higher consumption because of over-activation of complement in LN; (ii) there might be serum autoantibodies against CFH or a CFH gene mutation that may lead to dysfunction of CFH based on the findings of atypical haemolytic uraemic syndrome [26]. A common SNP Tyr402His is located in SCR7 and affects the binding of CFH to the surfaces of host cells [27]. Therefore we further investigated serum CFH autoantibodies and analysed the CFH Tyr402His (rs1061170) polymorphism in these patients with LN.

In our current study, serum autoantibodies against CFH could not be detected in patients with LN, and the allele frequency of the common SNP Tyr402His of CFH was comparable to that of normal controls. However, we cannot totally exclude the possibility of autoimmune reactivity and aberrant genotyping of CFH in patients with LN. (i) There might be autoantibodies against CFH and also against CFH-related proteins, which belong to a CFH protein super-family and share some similar SCRs with CFH. The mole number of CFHR1 is much higher than that of CFH, and an in vitro study has demonstrated that autoantibodies can bind to CFHR1 [28]. According to the above study, we speculate that autoantibodies against CFH may exist as immune complexes. Therefore we could not detect them by ELISA. Improved assays are needed in future studies. (ii) There might be other mutations or SNPs on CFH or CFHRs such as CFHR1 and CFHR3 in recent reports [14, 26, 29]. These need further investigation. For the genetic analysis, we calculated that the statistical power was 0.16 between Tyr402His and LN in our study. Generally the statistical power should be no less than 0.8 in clinical genetic research [30]. However, in our study, if the statistical power was assumed to be 0.8, the sample size should be 1570, and that may have contributed to the negative results. A large cohort of patients with LN is needed in further studies. As for the higher serum CFH levels in patients with active SLE without clinical evidence of LN than in normal controls, we speculate that hepatic synthesis of CFH might be up-regulated in active SLE without LN and serum CFH would return to nearly normal when patients achieve remission. However, once the kidneys are involved, the balance between production and consumption of CFH is broken and this contributes to the lower serum CFH in active LN. This also indicated that serum CFH might be a potential biomarker for early identification of LN in patients with SLE.

With the 2003 ISN/RPS LN classification, we evaluated the associations between serum CFH levels and renal histopathological characteristics. First, the serum CFH levels were significantly different in patients with various pathological classes of LN. Interestingly, the serum CFH levels in class III and subclass IV-S were the lowest among all the classes and subclasses. Further analysis showed that serum CFH levels were negatively associated with total activity indices, endocapillary hypercellularity and leucocyte infiltration, which indicated that the lower the serum CFH level, the more active the renal pathologic injury. Although the r values were not strong enough, the tendency might highlight the further work verified by larger cohort. Many previous studies, including ours [31], suggest that class III and subclass IV-S might be a similar early stage of subclass IV-G. It has been suggested that the focal and segmental glomerular lesions in class III and subclass IV-S might be the consequence of vascular lesions [32, 33]. Interestingly, the four LN patients, with both proliferative lesions and thrombotic renal microangiopathy, presented with the lowest serum CFH levels among all the patients. The pathological analysis indicated that serum CFH levels might not only reflect LN activity, but may also indicate microvasculopathy.

Patients with SLE and LN may have secondary TMA. Recent studies have demonstrated that the deficiency or dysfunction of CFH is an important cause of TMA [26]. In our study, considering the associations between serum CFH level and LN activity, as well as microvascular lesions, we hypothesized that some patients with LN might have similar pathogenic mechanisms as atypical haemolytic uraemic syndrome. When the serum CFH levels or function decreased, the alternative C3-convertase (C3bBb) on the cell surface, such as glomerular endothelial cells, could not be fully inactivated, thus leading to the cascade of overt complement activation and finally forming a membrane attack complex to induce endothelial cell injury. More interestingly, our study found strong glomerular expression of CFH in patients with LN, whether serum CFH was high or low. This finding might indicate that alternative pathway recruitment was indeed important in the pathogenesis of LN [13].

In conclusion, our study showed that serum CFH levels might not only reflect LN activity, but may also indicate microvasculopathy. CFH might be a contributor to the pathogenesis of LN, which needs further investigation.

Rheumatology key messages

- Serum CFH levels in active LN were significantly low.
- Serum CFH levels might not only reflect LN activity, but may also indicate microvasculopathy.
- CFH might be a contributor to the pathogenesis of LN.
Online.

conflicts of interest.

2276
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References

Supplementary data

Supplementary data are available at Rheumatology Online.

Funding: This work was supported by grants from the Chinese 973 project (no. 2012CB517702), National Natural Science Foundation of China to Innovation Research Group (81021004), National Natural Science Foundation of China (no. 81100497) and Beijing Natural Science Foundation (no. 7102150).

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data are available at Rheumatology Online.

References


