Association of CD14 Promoter Gene Polymorphism and Chlamydia pneumoniae Infection

Hock-Liew Eng,1 Chih-Hung Chen,2 Chou-cho Kuo,3 Jin-Shang Wu,2 Chiou-Huey Wang,4 and Tsun-Mei Lin4

1Department of Pathology, Chang Gung University and Memorial Hospital, Kaohsiung Medical Center, Kaohsiung, and Departments of 2Neurology, 3Family Medicine, and 4Medical Technology, College of Medicine, National Cheng Kung University, Tainan, Taiwan, Republic of China; 4Department of Pathobiology, University of Washington, Seattle

Recent studies have suggested that Chlamydia pneumoniae infection is an important factor in the development of atherosclerosis. The C→T polymorphism in the CD14 promoter gene has been reported to regulate the density of CD14 expression on monocytes for the activation of monocytes to secrete inflammatory cytokines by lipopolysaccharide. We investigated this genetic marker and its association with C. pneumoniae infection. Among 315 healthy subjects, the distribution of the C→T polymorphism in the CD14 promoter gene was 14.9% for the CC genotype, 54.3% for the CT genotype, and 30.8% for the TT genotype. Among subjects with the 3 CD14 genotypes, 59.5%, 64.9%, and 78.3%, respectively, were seropositive for C. pneumoniae. With multiple logistic regression analysis, the odds ratio of C. pneumoniae infection was 2.08 for CD14 TT genotype (95% confidence interval, 1.18–3.69; P = .016). A significant association between the CD14 TT genotype and C. pneumoniae infection was found.

CD14, a pattern-recognition receptor for several microbial products (e.g., lipopolysaccharide [LPS], peptidoglycans, and lipoteichoic acid) [1], is a 55-kDa glycosyl-phosphatidylinositol membrane–anchored protein expressed mainly on monocytes and macrophages but also on neutrophils and hepatocytes [2]. At the molecular level, CD14 acts by transferring LPS and other bacterial ligands from circulating LPS-binding protein to the Toll-like receptor (TLR) 4–MD-2 signaling complex [3]. Engagement of this complex results in the activation of innate host defense mechanisms, such as the release of inflammatory cytokines, and in the up-regulation of co-stimulatory molecules, thus providing cues that are essential for directing adaptive immune response [4]. LPS-responsive cells that do not contain membrane-bound CD14 (mCD14), such as endothelial cells, epithelial cells, and astrocytes, become sensitive to low concentrations of LPS in the presence of soluble CD14 (sCD14) [5]. Recently, a polymorphism in the promoter region of the CD14 gene has been studied [6, 7]. This polymorphism is located within the Sp1 transcription factor–binding site [8] and consists of a single base exchange (C→T) at position −260 when an HaellII restriction site is introduced [9]. The C→T polymorphism in the CD14 promoter gene has been reported to regulate the density of CD14 expression on monocytes. The T variants of the −260 polymorphism can promote CD14 gene transcription and cause higher expression of CD14 on monocytes [9], which leads to an enhanced inflammatory response. Furthermore, subjects carrying the T allele have been shown to have significantly higher sCD14 levels than do carriers of the C allele [6, 10]. Therefore, the CD14 polymorphism could be a genetic factor responsible for interindividual differences in the susceptibility to bacterial infection.

Inflammation may be involved in the pathogenesis of atherosclerosis [11], and infectious agents that cause inflammation may play a role in the development of atherosclerosis [12, 13]. There is mounting evidence that atherosclerosis is strongly associated with chronic infection with Chlamydia pneumoniae, a ubiquitous, gram-negative, obligate intracellular bacterium found in the
human respiratory system [14, 15]. Most persons experience their first C. pneumoniae infection before adulthood, and reinfection is common [16]. C. pneumoniae establishes persistent infection in the lungs and disseminates infection to both healthy arteries and arteries with preexisting atheromatous lesions via monocytes [17]. This association has been demonstrated by seroepidemiological studies [14, 18], examination of atheromatous plaque specimens by molecular and isolation methods [19–21], in vitro experiments and animal models [22, 23], and, recently, preliminary antichlamydial antibiotic intervention studies [24, 25].

Although atherosclerosis is known to have a genetic basis [26–29], genetic factors involved in atherosclerosis associated with C. pneumoniae infection are unknown. The susceptibility and inflammatory response to C. pneumoniae infection may vary from person to person. C. pneumoniae LPS is able to bind to CD14 and activate monocytes. It also can exert effects on cells that lack mCD14 and mediate via sCD14, which is elevated in many chronic infections and inflammatory conditions. However, there are few reports on the association between C. pneumoniae infection and sCD14 levels. Because genetic background is important in determining susceptibility to certain bacterial infection for an individual and because CD14 is one of the major receptors for C. pneumoniae infection, we hypothesized that the polymorphism of the CD14 promoter gene that affects CD14 expression could account for interindividual variability in C. pneumoniae infection. In the present study, we investigate the association of C. pneumoniae infection and the C(−260)→T polymorphism in the CD14 promoter gene and whether C. pneumoniae infection is able to modulate sCD14 levels systemically.

SUBJECTS, MATERIALS, AND METHODS

Study subjects. We consecutively recruited 315 healthy subjects (age range, 21–87 years [mean ± SD, 53.67 ± 13.46 years]; 154 men and 161 women), who participated in a 2-day hospitalized routine physical check-up at National Cheng Kung University Hospital from 1 July to 31 December 2001. Informed consent was obtained from participants, and the study was approved by the National Cheng Kung University Hospital Research Ethics Committee. All subjects were interviewed regarding their histories of cardiovascular risk factors, including hypertension, diabetes mellitus, and cigarette smoking. Hypertension was defined as treated or systolic blood pressure >140 mmHg and/or diastolic pressure >90 mmHg. Diabetes was defined as treated or fasting blood glucose level >126 mg/dL or 2-h postprandial blood glucose level >200 mg/dL. Smoking habit was defined as current or former smokers. Subjects with previous history of stroke, myocardial infarction, peripheral arterial occlusion, and malignancies were excluded. Blood samples were obtained after an overnight fasting. Serum concentrations of total cholesterol, triglyceride, and high-density lipoprotein cholesterol were measured. Low-density lipoprotein cholesterol levels were calculated using the Friedewald formula. Buffy coat was collected for DNA extraction, and plasma samples were stored in −30°C until determination of C. pneumoniae antibody and sCD14 levels.

Serological test for C. pneumoniae infection. Specific IgG antibody to C. pneumoniae was determined by use of an indirect microimmunofluorescence test, as described by Wang and Grayston [30], using formalin-fixed elementary bodies of C. pneumoniae strain AR-39 (Washington Research Foundation) as the antigen. In brief, the antigen was mixed with homogenized normal yolk sac membrane and then dotted onto glass slides. The antigen was fixed with acetone for 15 min at room temperature. Serum samples were diluted 2-fold in PBS (pH 7.2) and applied at a dilution of 1:8 for antibody screening. When a screening test was found to be positive, further 2-fold dilutions to 1:512 were examined. The slides were incubated in a humid chamber for 30 min at 37°C and then were washed 3 times for 5 min with PBS. Fluorescein isothiocyanate–conjugated antiserum (specific rabbit anti–human immunoglobulin) were diluted, according to the manufacturer’s instruction (Dako), and applied to the slides. The slides then were incubated at 37°C for 1 h and washed as described above. Specimens displaying a bright uniform fluorescence associated with elementary bodies were considered to be positive, and the measurements were recorded. An IgG titer ≥1:16 was considered to be positive, and a titer ≥1:64 was defined as persistent infection [31].

Polymorphism analysis of the CD14 promoter gene. Genomic DNA was isolated from peripheral blood leukocytes after red blood cell lysis by use of the phenol-chloroform extraction method. To genotype a large number of subjects for the CD14 C(−260)→T polymorphism, a restriction-fragment assay was developed. Amplification of the 295-bp fragment of the CD14 promoter gene was performed with primers 5′-ATCATCCTTTTCCCAACC-3′ (forward) and 5′-AAGTCTTGGCCTGCCTCT-3′ (reverse), as described elsewhere [32]. The polymerase chain reaction (PCR) product (4 μL) was cleaved in appropriate buffer with 8 U of HaeIII restriction enzyme. The DNA fragments were separated by electrophoresis through a 2% agarose gel. Digestion of the PCR products yielded bands of 295 bp in TT homozygotes, 140 and 155 bp in CC homozygotes, and all 3 bands (140, 155, and 295 bp) in the heterozygotes. Two readers determined the CD14 genotype, and repeated genotyping was done when there was a disagreement.

Determination of plasma levels of sCD14. Plasma levels of sCD14 were measured with a Human sCD14 EIA kit (R&D Systems), according to the manufacturer’s instructions.

Statistical analysis. Any differences among the groups of healthy subjects were evaluated by Student’s t test for continuous variables and by χ² test for categorical variables. Logistic
Table 1. Demographic and clinical characteristics of subjects, by *Chlamydia pneumoniae* seropositivity.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Seronegative (n = 100)</th>
<th>Seropositive (n = 215)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>40.0</td>
<td>53.0</td>
<td>.031</td>
</tr>
<tr>
<td>Age, years</td>
<td>51.2 ± 13.3</td>
<td>56.1 ± 12.5</td>
<td>.002</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>25.0</td>
<td>24.7</td>
<td>.347</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>15.0</td>
<td>19.1</td>
<td>.379</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>14.0</td>
<td>21.4</td>
<td>.120</td>
</tr>
<tr>
<td>Fasting glucose level, mg/dL</td>
<td>103.2</td>
<td>105.2</td>
<td>.631</td>
</tr>
<tr>
<td>Cholesterol level, mg/dL</td>
<td>198.7</td>
<td>203.1</td>
<td>.363</td>
</tr>
<tr>
<td>Triglyceride level, mg/dL</td>
<td>129.1</td>
<td>132.1</td>
<td>.767</td>
</tr>
<tr>
<td>HDL level, mg/dL</td>
<td>56.4</td>
<td>55.9</td>
<td>.733</td>
</tr>
<tr>
<td>LDL level, mg/dL</td>
<td>116.4</td>
<td>120.8</td>
<td>.316</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>6744</td>
<td>6883</td>
<td>.568</td>
</tr>
</tbody>
</table>

**NOTE.** Data are mean ± SD, except where noted. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

A regression model was used to elucidate the associations of *C. pneumoniae* seropositivity and CD14 promoter gene polymorphisms. Differences were considered to be significant at P < .05. Results are presented as mean ± SD.

**RESULTS**

The overall *C. pneumoniae* IgG seropositivity rate of the study population was 68.3% (215/315). Table 1 summarized the clinical features and laboratory data of subjects with positive and negative *C. pneumoniae* antibodies. There were no significant differences in history of hypertension, diabetes mellitus, smoking habit, fasting glucose level, white blood cell count, and lipid profiles between these 2 groups. The seropositive group was predominantly male, and their mean age was 56.1 years, significantly older than the seronegative group (P = .002).

The distributions of CD14 promoter genotypes and the allelic frequencies of the polymorphism in the CD14 promoter gene in the current study and in studies by other investigators are shown in Table 2. In the present study, the distributions of genotypes of the C(−260)→T polymorphism in the CD14 promoter gene were 47 for CC (14.9%), 171 for CT (54.3%), and 97 for TT (30.8%). The expected genotype frequencies were 17.6% for C homozygotes, 48.8% for heterozygotes, and 33.6% for T homozygotes. Statistical analysis did not reveal a difference between the frequencies of the observed genotypes and those of the expected genotypes (P = .682), indicating that the study population is in Hardy-Weinberg equilibrium. The frequencies of C and T alleles in our study were 42% and 58%, respectively. Compared with results from other countries, the C allele frequency that we found in the present study is the lowest. The allelic frequencies were different significantly among Taiwan, Finland, and the Czech Republic (table 2).

The CD14 genotype distribution and the allelic frequencies in *C. pneumoniae*–seropositive and –seronegative groups are shown in Table 3. The percentage of *C. pneumoniae* seropositivity in CC, CT, and TT genotypes was 59.6% (28/47), 64.9% (111/171), and 78.4% (76/97), respectively (P = .029), and the overall prevalence of *C. pneumoniae* seropositivity was significantly higher among carriers of the T allele than among non-T allele carriers (P = .016). When we tested for a possible restriction of an association of *C. pneumoniae* infection and the CD14 C(−260)→T promoter gene polymorphism in men and women, we found that the frequency of the T allele was not significantly different between men (76.5%) and women (67.7%); however, after subgrouping the study population, significant differences in seropositivity were observed only in women of either TT genotype (P = .026) or those carrying the T allele (P = .029) (table 3). For further investigation of a possible age-dependent relation-
In subjects with persistent infection was significant (P < .051). However, in subjects with nonpersistent C. pneumoniae infection, the sCD14 plasma levels were higher in subjects bearing the CT plus TT genotype than in those with the homozygous CC genotype (P = .368). 

Table 3. Association of CD14 genotypes with seropositivity of Chlamydia pneumoniae infection.

<table>
<thead>
<tr>
<th>Category</th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>28/47 (69.5)</td>
<td>111/171 (64.9)</td>
<td>76/97 (78.3)</td>
<td>.029</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16/25 (64.0)</td>
<td>59/79 (74.7)</td>
<td>39/50 (78.0)</td>
<td>.42</td>
</tr>
<tr>
<td>Female</td>
<td>12/22 (54.5)</td>
<td>52/92 (56.5)</td>
<td>37/47 (78.7)</td>
<td>.026</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;54b</td>
<td>11/20 (55.0)</td>
<td>49/87 (56.3)</td>
<td>32/45 (71.1)</td>
<td>.222</td>
</tr>
<tr>
<td>≥54</td>
<td>17/27 (63.0)</td>
<td>62/84 (73.8)</td>
<td>44/52 (84.6)</td>
<td>.093</td>
</tr>
</tbody>
</table>

NOTE: Data are no. of seropositive subjects/total no. of subjects (%).

Table 4. Univariate and multiple logistic regression analysis of contributing factors for Chlamydia pneumoniae seropositivity.

<table>
<thead>
<tr>
<th>Analysis, variable</th>
<th>β</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysisa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD14 genotypeb</td>
<td>0.721</td>
<td>2.06 (1.18–3.59)</td>
<td>.011</td>
</tr>
<tr>
<td>Age</td>
<td>0.034</td>
<td>1.03 (1.01–1.06)</td>
<td>.002</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.289</td>
<td>1.33 (0.76–2.34)</td>
<td>.314</td>
</tr>
<tr>
<td>Hypertension</td>
<td>−0.584</td>
<td>0.56 (0.29–1.08)</td>
<td>.083</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.246</td>
<td>1.28 (0.63–2.61)</td>
<td>.500</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.324</td>
<td>1.38 (0.66–2.92)</td>
<td>.395</td>
</tr>
</tbody>
</table>

NOTE: CI, confidence interval; OR, odds ratio.

a Constant, 0.565.
b CC or CT = 0; TT = 1.
c Constant, −1.338.

The clinical manifestations of C. pneumoniae infection are highly variable, ranging from an unsymptomatic infection to chronic persistent infection. Therefore, it seems plausible that the course of the infection is influenced by factors in the host’s immune system. There is now increasing evidence that host genetics have an impact on the susceptibility to or severity of several infectious diseases. The present study is the first to examine the relationship between C. pneumoniae infection and the CD14 promoter gene polymorphism. The results showed that C. pneumoniae seropositivity was significantly higher among subjects carrying the TT genotype than among those with the CC or CT genotype. This polymorphism appears to influence individual susceptibility to C. pneumoniae infection.

The interaction of C. pneumoniae infection with other known risk factors of atherosclerosis has been documented elsewhere [33]. However, genetic factors involved in C. pneumoniae infection are rarely reported. Dahlen et al. [34] reported that HLA-DR-13a or HLA-DR-17 genotypes in combination with high lipoprotein(a) levels and C. pneumoniae seropositivity are more frequent in patients with coronary artery disease (CAD) than in healthy control subjects. A recent study showed that interleukin (IL)–1 gene polymorphisms appear to influence susceptibility to atherogenic effect of C. pneumoniae infection and act in synergy with the development of myocardial infarction associated...
This may explain why the prevalence of 

disequilibrium with the CD14 promoter gene polymorphism.

ors (IL-10 and transforming growth factor–

inflammation mediators (IL-10 and transforming growth factor–β), oxygen radicals, and nitric oxide are triggered [3]. C. pneumoniae infection and increased production of endotoxins (LPSs) stimulate the synthesis of interleukins and other growth factors in monocytes and endothelial cells [40–42], which may lead to a chronic inflammatory reaction, with increased adhesion of monocytes, leukocytes, and platelets to the vessel wall and, ultimately, to atherosclerosis and thrombosis. The T allele causes decreased affinity of Sp protein interactions at a guanine-cytosine box, which enhances transcriptional activity in monocytes [43]. Regulation of CD14 promoter gene expression thus may appear to be important in C. pneumoniae infection and its associated diseases. Unkelbach et al. [26] reported no significant association between this polymorphism and cardiovascular diseases (e.g., CAD), but TT homozygosity was associated with an increased risk of CAD in a subgroup of subjects with a low risk of coronary diseases. Hubacek et al. [9] demonstrated a significantly higher T allele frequency in survivors of myocardial infarction, and the density of monocyte membrane CD14 was higher in TT homozygotes than in subjects with other genotypes.

Several studies have found an association between C. pneumoniae infection and cardiovascular diseases or stroke [15, 44–46]. However, prospective studies have failed to find the association [47, 48]. Here, we propose a hypothesis to elucidate this discrepancy: the CD14 promoter gene polymorphism may be a confounding variable of the association between C. pneumoniae infection and cardiovascular diseases. In our present study, the T allele in the CD14 promoter gene appears to influence individual susceptibility to C. pneumoniae infection. If this hypothesis is true, it will be of great significance in identifying subjects with cardiovascular diseases who carry this allele. This is important, because C. pneumoniae infection can be controlled by treatment with antibiotics. These findings, however, need to be verified in larger studies and in different ethnic groups.

A major limitation of our study is that a cross-sectional study cannot establish causality; it shows some association and is hypothesis driven. Our study demonstrates that the Chinese population has a higher T allele frequency than does the white population and that the CD14 promoter polymorphism is associated with C. pneumoniae infection, especially in females. In addition, our data may not be applicable to other ethnic populations. However, the percentage of individuals susceptible to C. pneumoniae infection is higher in the Chinese population in Taiwan than in the western countries mentioned here [39]. A Czech group demonstrated that the T allele was associated with a higher density of mCD14 on monocytes in healthy volunteers [9]. They suggested that a C(−260)→T change in the promoter region affects the level of CD14 promoter gene expression. Their findings are consistent with our study of mCD14 expression among 86 healthy college students (data not shown). However, other groups have failed to find such a

Table 5. Soluble CD14 (sCD14) expression during Chlamydia pneumoniae infection, by CD14 promoter gene C(−260)→T polymorphism genotype.

<table>
<thead>
<tr>
<th>Subject group, by IgG titer</th>
<th>CC</th>
<th>CT + TT</th>
<th>Total</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>1284 ± 434</td>
<td>1499 ± 767</td>
<td>1468 ± 731</td>
<td>.021</td>
</tr>
<tr>
<td>C. pneumoniae IgG titer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1:16</td>
<td>1247 ± 463</td>
<td>1501 ± 837</td>
<td>1448 ± 778</td>
<td>.264</td>
</tr>
<tr>
<td>&gt;1:16</td>
<td>1312 ± 421</td>
<td>1499 ± 741</td>
<td>1476 ± 712b</td>
<td>.273</td>
</tr>
<tr>
<td>&lt;1:64</td>
<td>1228 ± 411</td>
<td>1541 ± 762</td>
<td>1496 ± 729</td>
<td>.051</td>
</tr>
<tr>
<td>&gt;1:64</td>
<td>1407 ± 479</td>
<td>1402 ± 776</td>
<td>1403 ± 736c</td>
<td>.634</td>
</tr>
</tbody>
</table>

NOTE. Data are mean ± SD plasma sCD14 levels in nanograms per milliliter.

* CC vs. CT + TT groups (Student’s t test).

b P = .781, C. pneumoniae IgG titer <1:16 vs. >1:16.

P = .368, C. pneumoniae IgG titer <1:64 vs. >1:64.

with C. pneumoniae infection [35]. Because these genetic markers were analyzed in patients suffering from cardiovascular disease, their association with C. pneumoniae infection may be coincidental, because both C. pneumoniae infection and these genetic markers are risk factors for cardiovascular diseases. In contrast, our results demonstrated an association between a CD14 promoter gene polymorphism and C. pneumoniae infection from apparently healthy subjects. Some biological basis must exist to explain this association; that is, CD14 polymorphism may influence the susceptibility to C. pneumoniae infection either directly or indirectly through another genetic marker that is in linkage disequilibrium with the CD14 promoter gene polymorphism.

The frequency of the T allele was 58% in our Taiwanese subjects and was 51% in Japanese subjects [36], both of which were higher than the frequency in white subjects (35%–48%) [9, 10, 37, 38]. This may explain why the prevalence of C. pneumoniae infection among Taiwanese subjects is higher than other populations [39].

CD14 is a glycosyl-phosphatidylinositol membrane-anchored cell-surface molecule that has been identified as a receptor for LPS [2]. After LPS binds to CD14, the production and release of proinflammatory cytokines (e.g., tumor necrosis factor [TNF], IL-1, IL-6, and IL-8), anti-inflammatory mediators (IL-10 and transforming growth factor–β), oxygen radicals, and nitric oxide are triggered [3]. C. pneumoniae infection and increased production of endotoxins (LPSs) stimulate the synthesis of interleukins and other growth factors in monocytes and endothelial cells [40–42], which may lead to a chronic inflammatory reaction, with increased adhesion of monocytes, leukocytes, and platelets to the vessel wall and, ultimately, to atherosclerosis and thrombosis. The T allele causes decreased affinity of Sp protein interactions at a guanine-cytosine box, which enhances transcriptional activity in monocytes [43]. Regulation of CD14 promoter gene expression thus may appear to be important in C. pneumoniae infection and its associated diseases. Unkelbach et al. [26] reported no significant association between this polymorphism and cardiovascular diseases (e.g., CAD), but TT homozygosity was associated with an increased risk of CAD in a subgroup of subjects with a low risk of coronary diseases. Hubacek et al. [9] demonstrated a significantly higher T allele frequency in survivors of myocardial infarction, and the density of monocyte membrane CD14 was higher in TT homozygotes than in subjects with other genotypes.
positive correlation between the CD14 promoter polymorphism and receptor density on monocytes [49, 50]. Some reasons for these conflicting results include, first, the possibility that the T allele in the CD14 promoter gene may be in linkage disequilibrium with other polymorphisms in other locations involved in the expression of CD14 [51], and, second, the fact that the growth of C. pneumoniae has been shown to induce cytokine production and expression of CD14 in human monocytes [52]. These findings need to be further clarified by reporter gene assays, which certainly will shed some more light on this genotype-phenotype association.

C. pneumoniae can establish persistent infection in monocytes or macrophages and disseminate systemically. mCD14 expression on monocytes may act as a receptor for C. pneumoniae infection; subjects with the TT genotype have greater expression of mCD14 and, thus, increased susceptibility to C. pneumoniae infection than do subjects with the CC genotype. Genetically determined increased expression of CD14 could be associated with a high response to LPS in affected subjects and could lead to an increased inflammatory reaction to C. pneumoniae infection, a process that may promote atherogenesis and plaque rupture. However, conflicting results on the association of this polymorphism with bacterial infection have been reported in the literature. Gibot et al. [7] demonstrated that the TT genotype of the CD14 promoter gene was associated with susceptibility to and outcome of septic shock. However, studies by Hubacek et al. [53], Heesen et al. [54], and Agnese et al. [55] did not find an association between this polymorphism and severe infections. Several reasons may account for these conflicting results. As stated above, a possible linkage disequilibrium between the −260 mutation and other variations may also mediate the mCD14 density and result in a change in infectious susceptibility [50]. The growth of C. pneumoniae has been shown to induce cytokine production and expression of CD14 in human monocytes [52], and other non-LPS components of C. pneumoniae have been shown to stimulate cytokine production through TLR-dependent pathways [56]. In addition, increased risk of gram-negative bacterial infections was associated not only with CD14 polymorphism but also with other genetic variations, such as human TLR-4 mutation, as reported by Agnese et al. [55].

In our present study, plasma sCD14 levels were significantly different between subjects with the CT plus TT and CC genotypes (P = .021). This result is in accordance with previous reports showing that the presence of the T allele was associated with an increase in sCD14 levels [6, 10]. In the group with nonpersistent C. pneumoniae infection, subjects with genotypes carrying the T allele had higher sCD14 levels than did subjects without the T allele, whereas persistent C. pneumoniae infection had no effect on sCD14 levels. In contrast, the trend of sCD14 elevation in proportion to disease severity was more prominent in subjects with the CC genotypes, but the possible significance of this finding is not clear.

In conclusion, this study provides evidence that genetic polymorphisms of the CD14 promoter gene may modulate the susceptibility of individuals to C. pneumoniae infection. The CD14-mediated cellular activation induced by chlamydial LPS and other proinflammatory mediators may provide further insight into the molecular mechanisms of infection that participate in atherogenesis and other inflammatory disorders. These findings also provide a potential explanation for conflicting evidence regarding the role of C. pneumoniae infection in cardiovascular diseases.

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