Evidence for Antigen-Driven T-Cell Response in Unstable Angina

Giuseppina Caligiuri, MD, PhD; Gabrielle Paulsson, PhD; Antonino Nicoletti, PhD; Attilio Maseri, MD; Göran K. Hansson, MD, PhD

Background—Activation of T cells and macrophages has been associated with unstable angina (UA), but whether this reflects specific immune responses remains unclear.

Methods and Results—We analyzed the repertoire and the length of complementarity-determining region 3 of the T-cell receptor (TCR) β-chain variable (BV) gene segments of activated lymphocytes in 23 patients with UA, 13 patients with chronic stable angina (CSA), and 6 normal control subjects. We also tested the proliferation of systemic T cells in response to autologous coronary plaque proteins, oxidized LDL, and Chlamydia pneumoniae as candidate antigens, in vitro. The activated T cell–TCRBV repertoire was perturbed in 13 (57%) of 23 UA patients versus 3 (23%) of 13 CSA patients (P<0.016) and was restricted to 6 (28%) of 21 expanded TCRBV families; all were significantly higher in UA than in CSA patients. At least one monotypic or oligotypic activated TCRBV population was found in 15 (65%) of 23 UA patients and in 3 (23%) of 13 CSA patients (P<0.001). Finally, T cells from UA patients, but not from CSA patients or normal control subjects, proliferated in response to autologous proteins from coronary culprit lesions and/or to oxidized LDL.

Conclusions—Our findings suggest that the T-cell response observed in UA patients is antigen-driven and directed to antigens contained in the culprit coronary atherosclerotic plaques.

Key Words: angina • ischemia • prognosis • lymphocytes • antigens

A growing body of evidence suggests that unstable angina (UA) is associated with local1 and systemic2,3 activation of the immune system. Atherosclerotic plaques contain large numbers of activated T cells, suggesting that immune mechanisms are important factors in the pathogenesis of the atherosclerotic background.4–6 Indeed, inflammatory cells infiltrate nearly all plaques,6,7 and culprit lesions of infarcted hearts appear to be particularly enriched in activated T lymphocytes.3 This suggests that acute T-cell activation may play a role in plaque instability and acute clinical manifestations of coronary atherosclerosis.8 Although circulating immune markers are also chronically elevated in patients with chronic stable angina (CSA),9 a transient burst of T-cell activation can be detected only in patients with UA,2,3 suggesting that immune factors might precipitate plaque complications, such as thrombus formation and vasoconstriction at the site of the culprit lesions.3 However, it has not yet been established whether the nature of the systemic immune response observed in UA is specific.

Antigen-driven T-cell responses are characterized by a restricted repertoire of the highly polymorphic T-cell antigen receptor (TCR).10 This receptor has variable portions in both its α and β chains. The latter, called BV segments, are commonly used as monotypic markers of T-cell populations. We have analyzed the TCRBV antigen and mRNA repertoire in activated T cells of patients with UA and, as control conditions, in patients with CSA and healthy (normal control [NC]) subjects and found that specific TCRBV types are expanded in patients with UA. Cellular immunologic studies have suggested that these expansions may be due to responses to specific antigens present in atherosclerotic culprit plaques.

Methods

Patients

Given the high variability of the TCRBV repertoire in the normal population, study patients were carefully selected to form very homogeneous groups. All patients with evidence of recent infectious disease, erythrocyte sedimentation rate >20 mm/h, fever, immunosuppressive drug therapy, immunologic disorders, known or suspected neoplastic diseases, congestive heart failure, valvular heart disease, left bundle branch block, evidence of left ventricular aneurysm, recent (<3 months) major trauma, surgery, myocardial infarction, or coronary revascularization (coronary angioplasty or bypass surgery) were excluded from the study. As a consequence of such restricted selection, the sample size was relatively small; therefore, the present findings should be considered as preliminary in nature.
UA Patients

Only patients with ECG-documented new onset (<2 days before admission) of severe UA and at least 1 coronary stenosis detected at angiography (>75% reduction of lumen diameter) were admitted to the study (n=23). All patients had experienced at least 2 episodes of angina at rest or 1 episode lasting >20 minutes during the last 24 hours, accompanied by transient ischemic ST-segment changes and no detectable rise in creatine kinase-MB levels or troponin T levels (to exclude microcrosis, only patients with troponin T levels <0.2 μg/L were included in the study). Full medical therapy, including β-blockers and/or calcium antagonists, low-dose aspirin, and continuous intravenous infusion of nitrates and heparin, was introduced on admission, and continuous ECG telemetry monitoring was applied to all patients during their stay in our Coronary Care Unit. UA patients were divided into 2 subgroups 2 days after hospitalization: patients responding to full medical therapy (resolving UA, n=13) and patients with a more severe UA and persistence of ischemic episodes at rest after 48 hours of full medical therapy (refractory UA, n=10).

CSA Patients

As controls for anginal instability, we selected 13 patients with exclusively effort-related angina, stable for at least 6 months, with a positive exercise stress test and at least 1 coronary stenosis detected at angiography (>75% reduction of lumen diameter). All patients were on low-dose aspirin and various combinations of nitrates, β-blockers, and/or calcium antagonists.

NC Subjects

Blood samples from 6 age-matched healthy subjects (normal ECG and echocardiogram and no evidence of atherosclerosis by echography of the carotid arteries) were used as nonatherosclerotic controls. Blood samples (10 mL of peripheral venous blood) were drawn in fasting conditions, between 8:00 and 10:00 AM and within 24 hours of hospital admission. All patients gave their written informed consent to participate in the study, which was approved by the Ethics Committee of our institution.

FACS Analysis of Circulating T Cells

Whole blood cells were lightly fixed, and red blood cells were lysed and washed twice before immunostaining. Cell suspensions were incubated with mouse anti-human CD3 or with 21 different murine monoclonal antibodies against the human TCRBV (AV2.3, BV3, BV5.1, BV5.2+5.3, BV5.3, BV6.7, BV6.1, and BV12.1, which were generously provided by B. Olsson, MTC, Karolinska Institute, Stockholm, Sweden, and BV2, BV9, BV11, BV13.1, BV13.6, BV14, BV16.7, BV17, BV18, BV20, BV22, BV24, BV25, BV26, BV27, BV29, BV30, BV32, BV33, BV34, BV37, BV377, and subsequent computer analysis (Genotyper, ABI/Perkin-Elmer), the differently sized peaks were separated, and their CDR3 size in codons was calculated.

Antigen-Specific T-Cell Activation

T-cell proliferation in vitro in response to candidate antigens was analyzed in a subset of six UA and 6 CSA patients undergoing atherectomy during the study as well as in 6 healthy controls. T-cell proliferative responses were assessed by using peripheral blood mononuclear cells (including T cells as well as antigen-presenting cells, such as monocytes/macrophages, dendritic cells, and B cells) in culture. Antigenic preparations were (1) soluble proteins from each individual atherectomy homogenate (plaque protein at 10, 50, and 100 μg/mL) or pooled together for culture with peripheral blood mononuclear cells from NC subjects, (2) *Chlamydia pneumoniae* outer membrane protein (OMP) complexes OMP-2 and MOMP3 (1, 5, and 10 μg/mL), and (3) copper-oxidized LDL14 (oxLDL at 1, 5, and 10 μg/mL). Frozen sterile atherectomy specimens were cryohomogenized and resuspended in culture medium. After centrifugation (14 000 rpm, 4°C, 30 minutes), the supernatants were collected and assayed for protein content (BCA method). Human serum albumin (10, 50 and 100 μg/mL) and phytomagglutinin (1, 5, and 10 μg/mL) served as negative and positive controls, respectively. Each antigen was added after 2 days of culture, and proliferation was assessed after 4 more days of culture and after addition of [H]thymidine 18 hours before harvesting.

Statistical Analysis

Data are expressed as mean±SEM. To determine whether the TCRBV repertoire of activated T cells was able to discriminate between groups, FACS data (percentages of TCRBV/DR+ cells) were submitted to principal component analysis (PCA) by use of IGOR software (WaveMetrics, Inc). PCA is a descriptive statistical method that permits the simultaneous analysis of many parameters for different groups of patients. The number of numerical variables to be analyzed is determined by the number of subjects (in our case, n=42) multiplied by the number of parameters (in our case, 21 TCRBV types). Such analysis would take into account 42×21=882 numerical variables. The aim of PCA is to obtain a representation in a fewer-dimension space compared with the initial number of dimensions (number of variables). For this purpose, the PCA finds those associations of variables (called factors) that best characterize the differences between groups. A factor is a linear combination of related variables (such as the different TCRBV types within the activated lymphocyte pool) that can take the place of the original variables in further analysis. The structure of the factors (the variables represented by each factor) is the most relevant information that results from PCA.
Expansion of Restricted TCRBV Families

Activated T Cells in UA Patients Originate From Expansion of Restricted TCRBV Families

Results

The percentage of CD3\(^+\)/DR\(^+\) cells in the FACS-gated lymphocyte population was significantly higher in UA patients \(7.8\pm1.1\%\) \((P<0.001)\) than in CSA patients \(3.8\pm0.3\%\) and healthy controls \(2\pm0.1\%\). In the UA subgroup analysis, refractory UA patients showed higher levels of this marker compared with resolving UA patients \(9.6\pm2.2\%\) versus \(6.4\pm1\%\), respectively; \(P<0.05\).

Thirteen \(57\%\) of 23 UA patients showed a perturbed TCRBV/DR\(^+\) repertoire, which was significantly different from the one observed in NC subjects \((P<0.05, \text{Figure 1})\). Conversely, only 3 \(23\%\) of 13 CSA patients showed a...

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**Table 1.** Percentages of TCRBV/DR\(^+\) Cells in UA Patients, CSA Patients, and NC Subjects

<table>
<thead>
<tr>
<th>TCRBV</th>
<th>NC (Mean±SD)</th>
<th>CSA (Mean±SD)</th>
<th>UA (Mean±SD)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.3</td>
<td>0.29±0.04</td>
<td>0.63±0.20</td>
<td>0.80±0.11</td>
<td>0.0071</td>
</tr>
<tr>
<td>2</td>
<td>0.28±0.07</td>
<td>3.89±1.57</td>
<td>2.89±0.61</td>
<td>0.0053</td>
</tr>
<tr>
<td>3</td>
<td>0.08±0.01</td>
<td>0.28±0.06</td>
<td>2.09±0.66(\dagger)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5.1</td>
<td>0.15±0.02</td>
<td>0.35±0.12</td>
<td>1.29±0.31(\dagger)</td>
<td>0.0057</td>
</tr>
<tr>
<td>5.2+5.3</td>
<td>0.08±0.01</td>
<td>0.26±0.07</td>
<td>0.90±0.02(\dagger)</td>
<td>0.0005</td>
</tr>
<tr>
<td>5.3</td>
<td>0.25±0.05</td>
<td>0.28±0.07</td>
<td>1.40±0.46</td>
<td>0.0065</td>
</tr>
<tr>
<td>6.7</td>
<td>0.59±0.19</td>
<td>1.36±0.37</td>
<td>1.11±0.34</td>
<td>0.7845 (NS)</td>
</tr>
<tr>
<td>8.1</td>
<td>0.15±0.03</td>
<td>0.85±0.39</td>
<td>0.74±0.11</td>
<td>0.0019</td>
</tr>
<tr>
<td>9</td>
<td>0.12±0.03</td>
<td>0.47±0.13</td>
<td>1.04±0.24(\dagger)</td>
<td>0.0021</td>
</tr>
<tr>
<td>11</td>
<td>0.18±0.04</td>
<td>0.53±0.16</td>
<td>0.92±0.27</td>
<td>0.0398</td>
</tr>
<tr>
<td>12.1</td>
<td>0.19±0.05</td>
<td>0.81±0.25</td>
<td>1.28±0.28(\dagger)</td>
<td>0.0172</td>
</tr>
<tr>
<td>13.1</td>
<td>0.29±0.07</td>
<td>0.56±0.18</td>
<td>1.07±0.36</td>
<td>0.2412 (NS)</td>
</tr>
<tr>
<td>13.6</td>
<td>0.19±0.06</td>
<td>0.39±0.13</td>
<td>1.16±0.34</td>
<td>0.0019</td>
</tr>
<tr>
<td>14</td>
<td>0.15±0.05</td>
<td>0.41±0.16</td>
<td>1.05±0.24(\dagger)</td>
<td>0.0018</td>
</tr>
<tr>
<td>16.1</td>
<td>0.34±0.09</td>
<td>0.66±0.10</td>
<td>1.78±0.69</td>
<td>0.047</td>
</tr>
<tr>
<td>17</td>
<td>0.26±0.13</td>
<td>0.42±0.13</td>
<td>1.21±0.34</td>
<td>0.0059</td>
</tr>
<tr>
<td>18</td>
<td>0.19±0.03</td>
<td>0.76±0.19</td>
<td>1.38±0.40</td>
<td>0.001</td>
</tr>
<tr>
<td>20</td>
<td>0.17±0.04</td>
<td>0.69±0.20</td>
<td>1.86±0.52</td>
<td>0.0013</td>
</tr>
<tr>
<td>21.3</td>
<td>0.22±0.10</td>
<td>0.78±0.22</td>
<td>0.88±0.16</td>
<td>0.0925 (NS)</td>
</tr>
<tr>
<td>22</td>
<td>0.10±0.03</td>
<td>0.52±0.13</td>
<td>0.68±0.16</td>
<td>0.0179</td>
</tr>
<tr>
<td>23</td>
<td>3.44±0.23</td>
<td>4.88±1.04</td>
<td>7.20±1.06</td>
<td>0.1277 (NS)</td>
</tr>
</tbody>
</table>

*Kruskal-Wallis test; †significantly different from CSA (Fisher’s PLSD); ‡significantly different from NC (Fisher’s protected least significant difference).
perturbed TCRBV/DR^+ repertoire (P<0.05 versus UA patients), whereas the remaining 10 patients (77%) had a conserved normal TCRBV/DR^+ repertoire (overlapping the one observed in the NC subjects, Figure 1). Comparison of the percentage of TCRBV/DR^+ cells between the UA, CSA, and NC groups revealed that the proportion of 6 DR^+ TCRBV families was significantly increased in UA patients compared with CSA patients and/or NC subjects (Table 1). Although expanded TCRBV families were similar in the 2 UA subgroups, there was a tendency for a higher percentage of DR^+ /TCRBV3^ in UA patients (Table 2).

**UA Is Associated With Mono-Oligotypic Expansion of Activated T Cells**

At least one monotypic or oligotypic TCRBV-CDR3 peak (Figure 2) was detected in 15 of 23 UA patients versus 3 of 13 CSA patients (P<0.05). UA patients, but not CSA patients or NC subjects, showed monotypic expansions of BV3, BV5, BV12, BV17, and BV20 (all with P<0.01). Conversely, oligotypic expansions of BV9, BV14, and BV18 were found in 1, 2, and 3 patients with CSA, respectively, but not in UA patients or NC subjects. Table 3 illustrates the differences between UA and CSA patients in mono-oligotypic TCRBV expansions. At 3 months, 8 (32%) of the 25 total TCRBV-CDR3 skewed peaks were still detectable in UA patients (BV3 in 3 [43%] of 7, BV5 in 3 [100%] of 3, and BV17 in 2 [33%] of 6); the remaining 17 (68%) of 25 TCRBV-CDR3 peaks detected on admission in UA patients were no longer detected after 3 months (data not shown). In CSA patients, all the TCRBV-CDR3 skewed peaks observed on admission were still detectable at 3 months (data not shown).

**Figure 2.** Example of DR^+ /TCRBV^ analysis by FACS and reverse transcription PCR. Representative examples of FACS and reverse transcription PCR analysis of DR^+ T-cell repertoire in patients with UA are shown. Left, FACS dot plot in fluorescent channel within lymphocyte gate. The percentage of DR^+ /TCRBV3^ cells is displayed at top right of each plot. Right, CDR3 length analysis of TCRBV3 mRNA from DR^+ enriched cells. Top, Representative example of monotypic expansion of TCRBV3 in UA patients. Center, Representative example of polyclonal expansion of TCRBV3 in UA patients. Bottom, Negative control (CD3-negative selected cells).

### Discussion

An acute inflammatory state is statistically associated with a poor clinical outcome in UA. The inflammatory response observed in UA is not a mere consequence of plaque disruption, thrombosis, or myocardial ischemia, suggesting that inflammatory triggers may actually play an independent role in the pathogenesis of UA. The inflammatory triggers may be of an antigenic nature, because activation of the specific immunity is also detectable in UA and correlated to the clinical outcome. Thus, antigen-specific immune activation may, together with immunologically nonspecific inflammatory stimuli, determine the outcome of acute coronary syndromes. As recently pointed out, this resembles the

### Table 2. Percentages of TCRBV^+ /DR^+ Cells in Resolving and Refractory UA Subgroups

<table>
<thead>
<tr>
<th>TCRBV</th>
<th>Resolving UA</th>
<th>Refractory UA</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>a2.3</td>
<td>0.79±0.17</td>
<td>0.83±0.17</td>
<td>0.6418</td>
</tr>
<tr>
<td>2</td>
<td>1.90±0.35</td>
<td>4.20±1.24</td>
<td>0.2148</td>
</tr>
<tr>
<td>3</td>
<td>1.31±0.40</td>
<td>3.10±1.40</td>
<td>0.0721</td>
</tr>
<tr>
<td>5.1</td>
<td>1.34±0.45</td>
<td>1.23±0.45</td>
<td>0.8768</td>
</tr>
<tr>
<td>5.2+5.3</td>
<td>0.95±0.30</td>
<td>0.85±0.37</td>
<td>0.8041</td>
</tr>
<tr>
<td>5.3</td>
<td>1.42±0.53</td>
<td>1.39±0.83</td>
<td>0.5767</td>
</tr>
<tr>
<td>6.7</td>
<td>1.18±0.56</td>
<td>1.02±0.39</td>
<td>0.3685</td>
</tr>
<tr>
<td>8.1</td>
<td>0.66±0.14</td>
<td>0.85±0.18</td>
<td>0.4568</td>
</tr>
<tr>
<td>9</td>
<td>0.87±0.26</td>
<td>1.61±0.45</td>
<td>0.5351</td>
</tr>
<tr>
<td>11</td>
<td>1.08±0.44</td>
<td>0.70±0.26</td>
<td>0.5981</td>
</tr>
<tr>
<td>12.1</td>
<td>1.42±0.27</td>
<td>1.09±0.56</td>
<td>0.0628</td>
</tr>
<tr>
<td>13.1</td>
<td>1.05±0.50</td>
<td>1.16±0.48</td>
<td>0.3211</td>
</tr>
<tr>
<td>13.6</td>
<td>1.17±0.50</td>
<td>1.16±0.48</td>
<td>0.9259</td>
</tr>
<tr>
<td>14</td>
<td>0.85±0.23</td>
<td>1.31±0.47</td>
<td>0.5149</td>
</tr>
<tr>
<td>16.1</td>
<td>1.28±0.28</td>
<td>2.43±1.56</td>
<td>0.6869</td>
</tr>
<tr>
<td>17</td>
<td>0.86±0.19</td>
<td>1.66±0.75</td>
<td>0.9753</td>
</tr>
<tr>
<td>18</td>
<td>1.02±0.21</td>
<td>1.85±0.88</td>
<td>0.6642</td>
</tr>
<tr>
<td>20</td>
<td>2.01±0.68</td>
<td>1.65±0.86</td>
<td>1.1366</td>
</tr>
<tr>
<td>21.3</td>
<td>0.88±0.14</td>
<td>0.89±0.33</td>
<td>0.5351</td>
</tr>
<tr>
<td>22</td>
<td>0.55±0.13</td>
<td>0.84±0.34</td>
<td>0.8041</td>
</tr>
<tr>
<td>23</td>
<td>5.87±0.88</td>
<td>8.92±2.08</td>
<td>0.3853</td>
</tr>
</tbody>
</table>

*Mann-Whitney U test. TCRBV 3 tended to be higher in refractory UA, whereas TCRBV 12.1 tended to be higher in resolving UA.*
situation in rheumatoid arthritis, a disease that shares many pathogenetic features with atherosclerotic vascular disease.\textsuperscript{22}

In the present study, we found that the antigen receptor repertoire of the activated T cells is skewed in 57\% of patients with UA versus 23\% of patients with CSA, supporting the hypothesis that an antigen-driven immune response may play a role in the pathogenesis of clinical instability of angina pectoris.

The antigenic triggers might be located at the site of the culprit lesion, because a specific proliferative response to proteins contained in the atherectomy specimens of UA patients but not CSA patients or NC subjects was detected. The composition of unstable plaques is complex, and the large number of potential antigenic epitopes may explain the variability in the TCR selection of activated T cells in different patients. Indeed, it has been demonstrated that the plaque-infiltrating T cells are polyclonal, which may reflect the variable antigenic background in the atherosclerotic lesions.\textsuperscript{23,24} However, during the acute phases of plaque instability, some plaque antigens may elicit a transient, specific, systemic immune response. Indeed, we found that <5 (23\%) of 21 TCRBV types are significantly expanded in each UA patient, indicating that such dynamic T-cell activation is not polyclonal. More important, expanded activated TCRBV\textsuperscript{1} cells showed monotypic or oligotypic CDR3 peaks in 65\% of UA patients. This clearly suggests activation by a limited number of antigenic epitopes. In particular, monotypic expansions of TCRBV3 and TCRBV17 were found in 8 patients with UA (4 and 4, respectively), but none were observed in CSA patients or NC control subjects. Interestingly enough, 17 (68\%) of 25 total monotypic or oligotypic TCRBV-CDR3 peaks were no longer detectable after 3 months from the waning of symptoms in UA patients, suggesting that antigen-specific T-cell populations were transiently activated and confined to the clinically unstable phases of angina.

Conversely, expanded DR\textsuperscript{1}/TCRBV\textsuperscript{1} populations were polyclonal in the majority (77\%) of CSA patients, thus confirming the greater antigenic variability of the T-cell response related to the chronic atherosclerotic background. Interestingly enough, the skewed TCRBV genes in CSA patients were different from those in UA patients, suggesting that different antigenic epitopes may be related to the chronic T-cell activation observed in CSA patients.

Because complicated atherosclerotic plaques contain both oxLDL and \textit{C pneumoniae}, we tested the hypothesis that the T-cell response observed in UA might be targeted to these 2 plaque antigenic proteins among the large number of potential plaque antigens.

Previous studies have shown that patients with UA present elevated levels of oxLDL in their blood,\textsuperscript{25} and oxLDL-specific T-cell clones have been isolated from complicated atherosclerotic plaques.\textsuperscript{14} In the present study, the proliferative response of T cells to oxLDL was significantly increased in patients with UA compared with patients with CSA, although data showed considerable overlap. Interestingly,

\begin{table}
\centering
\caption{Monotypic and Oligotypic Expansions of DR\textsuperscript{1} TCRBV Families in UA and CSA}
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Gene & UA & & & CSA & & \\
 & Total & Mono & Oligo & Total & Mono & Oligo \\
\hline
BV3 & 7 & 4 & 3 & 0 & 0 & 0 \\
BV5 & 3 & 1 & 2 & 0 & 0 & 0 \\
BV9 & 2 & 0 & 2 & 1 & 0 & 1 \\
BV12 & 1 & 1 & 0 & 0 & 0 & 0 \\
BV14 & 2 & 0 & 2 & 2 & 1 & 1 \\
BV17 & 6 & 4 & 2 & 0 & 0 & 0 \\
BV18 & 0 & 0 & 0 & 3 & 2 & 1 \\
BV21 & 4 & 2 & 2 & 0 & 0 & 0 \\
\hline
\end{tabular}
\begin{tabular}{l}
Total indicates number of monotypic and oligotypic skewed CDR3 peaks; Mono, number of monotypic CDR3 peaks; and Oligo, number of oligotypic CDR3 peaks. \\
*\textsuperscript{*}x\textsuperscript{2} test.
\end{tabular}
\end{table}
patients with a more severe UA, refractory to the full medical therapy, showed a marked proliferative response to oxLDL compared with the response in patients with a more favorable outcome (resolving UA) or with control subjects. However, a positive response to oxLDL was usually associated with a positive response to the other antigenic preparations also, suggesting that plaque antigens other than oxLDL may also be involved in the T-cell response observed in UA.

A proliferative response to C pneumoniae antigens was detectable in stable and unstable patients, possibly reflecting a role for a specific response to this ubiquitous pathogen in the pathogenesis and/or the progression of atherosclerosis. This is in line with the results of an increasing number of serological studies. However, no differences could be observed between UA and CSA patients. Thus, our results do not support a role for C pneumoniae in the pathogenesis of plaque instability, although we cannot rule it out because of the relatively small sample population of the present study.

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