Complement Receptors and Regulatory Proteins in Human Atherosclerotic Lesions

Paul S. Seifert and Göran K. Hansson

Complement activation in human atherosclerotic lesions is indicated by the presence of C5b-9 terminal complexes. By using monoclonal antibodies to the complement C3b receptor (CR1) and the IC3b receptor (CR3), it was observed that approximately 20% of the cells in complicated human carotid lesions express CR1 and CR3 antigens. One to five percent of complement receptor-positive cells stained for smooth muscle cell-specific myosin, and the remainder were determined to be predominantly macrophages, based on their reactivity to anti-LeuM3 (CD14) monoclonal antibody. No C3dg receptor (CR2)-positive cells were observed in any of the eight lesions examined. The complement regulatory glycoprotein decay accelerating factor (DAF) was widely distributed extracellularly, in addition to being present on 20% to 60% of the total cell population. Factor H, a plasma protein that regulates alternative pathway C3 convertase formation, was observed extracellularly in 70% of the lesions examined. C1 Inhibitor was present in a few plaque specimens, was relatively sparse, and appeared largely cell associated. Terminal C5b-9 complement complexes were pervasive in all lesions. Both the complement regulatory proteins and the activation products were limited to the area of lesion involvement and were absent from normal arterial wall. The results demonstrate that molecules involved in complement regulation and complement ligand binding are present in atherosclerotic lesions, where they may function to modulate the activities of complement.


The pathogenesis of atherosclerosis centers upon the interactions between blood and the arterial wall. The complement system consists of approximately 16 plasma proteins, and their participation in atherosclerosis is suggested by the presence in lesions of native complement proteins and C5b-9 terminal complexes.

Terminal complement complexes arise as a final product of the complement activation sequence, and their assembly from native C5 through C9 proteins involves neoantigen formation, i.e., creation of unique antigenic epitopes not present on the native unassembled proteins. Thus, immunological detection techniques utilizing antibodies to C5b-9 neoantigens reliably indicate that complement activation has taken place.

Activation of complement is controlled at each step in the activation sequence. Eleven distinct proteins with complement regulatory activity have been described. Seven of the regulatory proteins are fluid-phase molecules and four are cell membrane glycoproteins. At present, the complement regulatory mechanisms operable in atherosclerotic lesions are unknown. Macrophages, a common component of lesions, possess cell surface complement regulatory molecules; in addition, they are capable of synthesizing soluble complement regulatory proteins. Whether they do so in atherosclerotic lesions, however, has not been documented. It is unknown at present whether vascular smooth muscle cells (SMC) synthesize or express any complement regulatory proteins.

Activation of the complement system may influence atherosclerotic development, since complement activation fragments modulate various macrophage functions, e.g., phagocytosis, chemotaxis, adhesion, and lysosomal degranulation. Furthermore, formation of C5b-9 complexes on cell membranes can lead to arachidonic acid metabolism, platelet activation, and cell death.

In the present report, we provide evidence for cellular and extracellular complement regulatory proteins in human atherosclerotic lesions as well as in cells possessing complement receptors. The confinement of complement regulatory proteins to diseased areas of the arterial wall suggests a response to local complement activation. Complement may influence lesion development via ligand binding of activation products to cells bearing complement receptors.

Methods

Antibodies

The primary antibodies used in this study are summarized in Table 1. They were detected with anti-species-specific antisera (anti-mouse immunoglobulin G [IgG] produced in sheep, anti-rabbit IgG produced in swine) conjugated with fluorescein (FITC), rhodamine (Dakopatts, Copenhagen, Denmark), or biotin (Amersham, Amersham, Sweden).
were mounted in PBS containing glycerol and p-pherv this step. After the final three rinses in PBS, the sections
were exposed to a species-specific secondary antibody at
a dilution of 1:200. Alternatively, a rhodamine-conjugated anti-
body was applied for 15 minutes, the tissue was rinsed three
times with PBS, followed by a Texas red- or FITC-conjugated
secondary antibody and then incubated on the
sections in a humidity chamber for 30 minutes. After three
rinses in PBS, biotinylated anti-species-specific Ig was
applied for 15 minutes, the tissue was rinsed three times
in PBS, and then the sections were incubated in PBS
containing biotinylated goat anti-rabbit IgG, followed by
treatment with peroxidase-conjugated streptavidin for
15 minutes. After rinsing three times in PBS, the sections
were incubated in 3% hydrogen peroxide for 10 minutes.
Aminoethylcarbazole was used as a chromogen.

Immunohistochemistry

Frozen sections of arterial tissue were fixed with
95% ethanol for 10 minutes and were rinsed three times in
phosphate-buffered saline (PBS), pH 7.4.22 Heat-
inactivated normal horse serum (Vector, Buriingham, CA)
was applied to the sections before incubation with primary
antibodies. The sections were incubated in PBS containing
900 U/ml collagenase (Type IV, Sigma, St. Louis, MO), 90 U/ml elastase
(Sigma), 1 mg/ml soybean trypsin inhibitor (Sigma), and
0.9 mM CaCl₂ (pH 7.4). After 2-hour incubation and
mixing at room temperature, the supernatant was
harvested and recentrifuged at 11 000 g for 10 minutes.
A decidualizing agent for tissue sections was incubated once more with
enzymes solution, thus providing a total of three extraction
methods.

SMC myosin

Factor H

Factor B

C3

C1q

DAF

C5b-9 neoantigen

Table 1. Antibodies Used in This Study

<table>
<thead>
<tr>
<th>Antibody against</th>
<th>Source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1 (J3D3)</td>
<td>ImmunoTech, Marseille, France</td>
<td></td>
</tr>
<tr>
<td>CR2 (HB-5)</td>
<td>Becton Dickinson, Mountain View, CA</td>
<td></td>
</tr>
<tr>
<td>CR3 (D12)</td>
<td>Becton Dickinson</td>
<td></td>
</tr>
<tr>
<td>CD14 (LeuM3)</td>
<td>Becton Dickinson</td>
<td></td>
</tr>
<tr>
<td>C1 Inhibitor</td>
<td>Atlantic Antibodies, Scarborough, ME</td>
<td></td>
</tr>
<tr>
<td>Factor H</td>
<td>Atlantic Antibodies</td>
<td></td>
</tr>
<tr>
<td>Factor B</td>
<td>Atlantic Antibodies</td>
<td></td>
</tr>
<tr>
<td>Properdin</td>
<td>Atlantic Antibodies</td>
<td></td>
</tr>
<tr>
<td>C3t</td>
<td>Dakopatts, Copenhagen, Denmark</td>
<td></td>
</tr>
<tr>
<td>Clq</td>
<td>Dakopatts</td>
<td></td>
</tr>
<tr>
<td>SMC myosin</td>
<td>D. Larson, Boston, MA</td>
<td>48</td>
</tr>
<tr>
<td>DAF</td>
<td>V. Nussenweig, New York, NY</td>
<td>12</td>
</tr>
<tr>
<td>C5b-9</td>
<td>S. Bhakdi, Giessen, FRG</td>
<td>9</td>
</tr>
</tbody>
</table>

SMC = smooth muscle cell, DAF = decay accelerating factor.

In the latter case, they were further developed with
FITC or Texas red-conjugated Streptavidin (Amersham).

Arterial Tissue

Internal carotid and femoral arteries were obtained during
endarterectomy from patients experiencing transitory ischemic attacks.
Nonatherosclerotic arterial tissue was obtained from uterine arteries during hysterectomy. Carotid
and femoral specimens were transported to the laboratory
in ice-cold Hanks’ balanced salt solution, were immediately
embedded in OCT compound (Miles Laboratories Incorpo-
rated, Naperville, IL), and were snap-frozen in liquid nitro-
gen–cooled n-hexane. Tissue samples were stored at
-70°C until frozen sections were made.22 Uterine arteries
were dissected from the uterine wall and 1 to 2 mm long
sections were embedded in OCT and were snap-frozen.

Immunohistochemistry

Frozen sections of arterial tissue were fixed with
95% ethanol for 5 minutes and were rinsed three times in
phosphate-buffered saline (PBS), pH 7.4.22 Heat-
inactivated normal horse serum (Vector, Burlington, CA)
was applied to the sections before incubation with primary
antibodies. The sections were incubated in PBS containing
900 U/ml collagenase (Type IV, Sigma, St. Louis, MO), 90 U/ml elastase
(Sigma), 1 mg/ml soybean trypsin inhibitor (Sigma), and
0.9 mM CaCl₂ (pH 7.4). After 2-hour incubation and
mixing at room temperature, the supernatant was
harvested and recentrifuged at 11 000 g for 10 minutes.
A decidualizing agent for tissue sections was incubated once more with
enzymes solution, thus providing a total of three extraction
methods.

SMC = smooth muscle cell, DAF = decay accelerating factor.

In the latter case, they were further developed with
FITC or Texas red-conjugated Streptavidin (Amersham).
tions, areas positive for CR1 were observed to stain with anti-LeuM3 (CD14 antigen), a macrophage-specific monoclonal antibody. CR1-positive cells did not appear to be preferentially located to a particular region of the lesion.

Lesions wherein CR1-positive cells also stained with anti-SMC–specific myosin antibodies were observed (Figure 2). Such cells were observed in the fibrous cap as well as in lipid-rich areas. They were commonly located within fibrous lacunae and showed a linear granular staining pattern. Ross et al.24 and Gown et al.25 have determined that the majority of these pancake-like objects in fibrous lacunae are SMCs. The size, shape, anti-myosin reactivity, and location within lacunae suggest that these CR1-positive cells were SMCs.

To confirm that the anti-SMC–specific myosin antibodies did not react with monocyte/macrophages, frozen sections of normal human lymph node, blood smears, and 7-day-old cultured monocytes were stained with anti-SMC–specific myosin and anti-CR1. In all three cases, no CR1-positive cells were observed to react with anti-SMC–specific myosin antibodies.

CR3 was found in the same locations as CR1 (determined in consecutive sections, Figure 1) on approximately the same percentage of cells as CR1 (Table 3). Like CR1, CR3 was occasionally observed to co-localize with SMC-myosin positive cells (data not shown); however, the majority were myosin-negative. The results suggested that the CR1-positive cells were also CR3-positive (although this was not directly confirmed), and that the vast majority of complement receptor-bearing cells were leukocytes. No CR2-specific staining was observed in any of the eight lesion samples examined (Figure 1). Normal arterial tissue, located either adjacent to lesions or in normal uterine artery, exhibited no staining for CR1, CR2, or CR3.

Decay Accelerating Factor

Decay accelerating factor (DAF) is a cell membrane glycoprotein that can be released from its glycolipid anchoring tail by phospholipase C.26 It is also found in soluble form in body fluids, including plasma.27 Anti-DAF–specific immunofluorescence was observed celluarly and extracellularly in all 19 lesions examined (Figure 3 and Table 3). Extracellular DAF staining occurred on connective tissue fibers in a diffuse staining pattern and as granular deposits in tissue spaces. It was present throughout the lesion area. Cellular DAF staining varied from 20% to 60% of the cell population and correlated with both SMC and macrophage cell markers. Both cellular and extracellular DAF was confined to the area of the lesion. Normal arterial tissue was negative for DAF except at the lumen, consistent with the previously reported finding that only endothelial cells express DAF in normal blood vessels.27,28

Factor H

Factor H is a plasma protein that inhibits C3 convertase formation, in part by competing with Factor B for binding to C3b.29–33 Polyclonal antiserum directed to Factor H exhibited

Table 2. Summary of Function and Cellular Distribution of Complement Regulatory Proteins and Receptors

<table>
<thead>
<tr>
<th>Complement proteins</th>
<th>Function</th>
<th>Cellular distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1</td>
<td>Binds C4b, C3b, IC3b; cofactor for Factor I–mediated C3b/C3d degradation; promotes dissociation of C3 convertase; assists phagocytosis</td>
<td>Monocytes/macrophages; neutrophils; B lymphocytes; CD4 T lymphocytes; erythrocytes; follicular dendritic cells; glomerular podocytes</td>
</tr>
<tr>
<td>CR2</td>
<td>Binds C3dg</td>
<td>B lymphocytes</td>
</tr>
<tr>
<td>CR3</td>
<td>Binds IC3b; assists phagocytosis</td>
<td>Monocytes/macrophages; neutrophils; cytotoxic T lymphocytes</td>
</tr>
<tr>
<td>DAF</td>
<td>Inhibits C3/C5 convertase formation and accelerates the decay of preformed convertase</td>
<td>Leukocytes; erythrocytes; platelets; endothelium; epithelium</td>
</tr>
<tr>
<td>Factor H</td>
<td>Cofactor for Factor I–mediated cleavage of C3b into iC3b; competes with Factor B for C3b binding sites on convertases, thereby inhibiting convertase formation</td>
<td>Plasma protein</td>
</tr>
<tr>
<td>C1 inhibitor</td>
<td>Prevents autoactivation of C1; assists inactivation of activated C1</td>
<td>Plasma protein</td>
</tr>
<tr>
<td>Properdin</td>
<td>Stabilizes the C3 convertase, thus prolonging its half-life</td>
<td>Plasma protein</td>
</tr>
</tbody>
</table>

DAF = decay accelerating factor.

Table 3. Summary of Prevalence of Complement Proteins in Atherosclerotic Lesions

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Percentage of cells expressing antigen</th>
<th>Number of lesions with antigen/total number of lesions examined</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1</td>
<td>20±8</td>
<td>12:21</td>
</tr>
<tr>
<td>CR2</td>
<td>0</td>
<td>0.8</td>
</tr>
<tr>
<td>CR3</td>
<td>18±6</td>
<td>10:18</td>
</tr>
<tr>
<td>DAF</td>
<td>20 to 60</td>
<td>17:17</td>
</tr>
<tr>
<td>Factor H</td>
<td>—</td>
<td>5.7</td>
</tr>
<tr>
<td>Factor B</td>
<td>—</td>
<td>2.8</td>
</tr>
<tr>
<td>Properdin</td>
<td>—</td>
<td>3.6</td>
</tr>
<tr>
<td>C1 inhibitor</td>
<td>—</td>
<td>5.8</td>
</tr>
<tr>
<td>C3b-9</td>
<td>—</td>
<td>3.4</td>
</tr>
<tr>
<td>Clq</td>
<td>—</td>
<td>18:18</td>
</tr>
</tbody>
</table>

The percentage of antigen-positive cells was calculated by counting positively stained cells in four randomly chosen fields of view and dividing the obtained value by the number of total cells in the same field of view. Areas containing fewer than 20 cells were not considered.
Figure 1. Consecutive sections demonstrating complement receptor antigen in the tunica intima of a carotid artery atherosclerotic lesion. A. CR1. B. Myosin. C. CR3. D. CD14 (anti-macrophage). E. CR2 antigens. CR1 and myosin are a double stain of the same section photographed with fluorescein and rhodamine-specific filters, respectively. The CR1-expressing cells contain no myosin. CR3 and CD14 are found in the same general area (adjacent to the lumen) as CR1, but not myosin, suggesting that complement receptor-expressing cells are macrophages. Lack of CR2 (E) indicates that no B lymphocytes are present and demonstrates that nonspecific secondary antibody binding did not occur. The anti-macrophage (D) stain was performed with immunoperoxidase and hematoxylin to demonstrate the cellular nature of the reaction product (CD14 stain, open arrows; hematoxylin stain, arrows). All photomicrographs x300.
Figure 2. Carotid artery lesion double-labeled with antibodies against CR1 and smooth muscle cell (SMC) myosin. A number of cells stained for both CR1 and SMC myosin (arrowheads). A. CR1-specific fluorescence. B. SMC myosin-specific fluorescence. x600. The lumen is in the upper left. Some cells stained for CR1 but not myosin (arrows) and some for SMC myosin but not CR1 (double arrows). x600

Figure 3. High-magnification view of decay accelerating factor deposits (arrows) in the fibrous cap of a carotid artery atherosclerotic lesion. x600

Factor B (made using consecutive sections) was apparent. As shown in Figure 4, Factor H was at times found within the same location as C5b-9 but was always less extensive. No Factor H staining was present in normal arteries.

The amount of Factor H extractable from lesions by saline or collagenase treatment ranged from 14 μg of Factor H per gram (wet weight tissue) to 105 μg of Factor H per gram of tissue (Table 4). A second successive collagenase treatment revealed that an appreciable amount (75 μg/g) of Factor H still remained in the tissue.

**Properdin and C1 Inhibitor**

Properdin stabilizes the alternative pathway, C3 convertase, preventing its spontaneous decay and thereby prolonging its half-life. In addition, it protects the convertases from degradation by Factor I.34,35 C1 inh prevents autoactivation of C1 and assists in its inactivation after activation.36 Properdin and C1 inh were observed in some lesions (Table 3). However, in all positive cases the collective area of antigen-specific staining was small, and no sites of predilection were discerned. As shown in Figure 5, C1 inh appeared to be associated mainly with cells (presumably macrophages since they synthesize C1 inh32) and, further, with only a subpopulation of cells. C1 inh, but not properdin, was detected in extracts of lesions by rocket immunoelectrophoresis (Table 4). Neither properdin nor C1 inh was observed in normal arterial tissue.

**Factor B**

Factor B binds to C3b and is cleaved by Factor D to generate a C3 convertase, i.e., an enzyme capable of cleaving native C3. By double-staining for C3 and Factor B, it was estimated that less than 25% of the total C3/B was in the form of co-deposits. Staining for both
Figure 4. Carotid artery lesion labeled with antibodies against C5b-9 and Factor H. A. C5b-9 complexes were located throughout the lesion as granular masses or in linear arrays. ×300. B. Factor H antigen was less prevalent than C5b-9 and formed fine thread-like deposits. ×300

Table 4. Semiquantitative Analysis of Complement Regulatory Proteins in Lesion Extracts

<table>
<thead>
<tr>
<th>Patient</th>
<th>Factor H</th>
<th>Factor B</th>
<th>C1 inhibitor</th>
<th>Properdin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline extract</td>
<td>115</td>
<td>17</td>
<td>11</td>
<td>trace</td>
</tr>
<tr>
<td>Collagenase extract 1</td>
<td>139</td>
<td>9</td>
<td>7</td>
<td>*</td>
</tr>
<tr>
<td>Patient 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline extract</td>
<td>60</td>
<td>trace</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>Collagenase extract 1</td>
<td>105</td>
<td>*</td>
<td>5</td>
<td>*</td>
</tr>
<tr>
<td>Collagenase extract 2</td>
<td>75</td>
<td>*</td>
<td>5</td>
<td>*</td>
</tr>
</tbody>
</table>

Values are given as micrograms complement protein per gram of tissue (wet weight). Carotid artery atherosclerotic lesions were extracted first with saline and then by collagenase treatment. The quantity of complement protein in the extract was determined by rocket immunoelectrophoresis using normal human serum to generate the standard curve.

antigens was predominantly extracellular; however, occasional deposits were observed within fibrous lacunae, suggesting cellular deposition. In the latter case, C3 and B were found alone and as co-deposits. Factor B and C3 were occasionally observed in the same locations as C5b-9. Figure 6 depicts an example of this in the context of deposits, which appear largely cellular due to their position within fibrous lacunae. Factor B was observed in the majority of lesions examined (Table 3) but was not present in normal arterial wall. Immunoreactive Factor B was also detected in lesion extracts (Table 4).

C5b-9 Complexes

C5b-9 complexes were observed in every lesion examined (Table 2). The deposits were generally extensive and always limited to the area of lesion involvement. Most of the staining reaction appeared extracellular, occurring as amorphous granular masses (Figure 4). Linear granular staining within fibrous lacunae was also observed (Figure 6), suggesting cellular deposition.

As shown in Figure 6, C5b-9 deposits sometimes occurred in the same area as Factor B antigen. It may also be significant that this observation comes from an area
Figure 5. C1 inhibitor in a carotid artery atherosclerotic lesion. Near the lumen (top), several areas of C1 inh-specific immunofluorescence (A) (arrows) can be seen to correspond to nuclear hematoxylin staining (B) (arrows), indicating cellular C1 inhibitor expression. Deeper into the lesion, a region relatively devoid of cells (B) (arrowhead) exhibits C1 inhibitor staining (A), indicating extracellular C1 inhibitor. x75

adjacent to the necrotic core of the lesion. No obvious correlations were apparent between C5b-9 complexes and any of the complement regulatory proteins or receptors. C5b-9 was observed in the intimal thickenings of aged arteries, but not within the media.

Discussion

The demonstration of C5b-9 terminal complement complexes in human atherosclerotic lesions with monoclonal and polyclonal antibodies to C5b-9 neoantigens implicates complement activation in atherogenesis. Our observations in this regard confirm those previously reported and have extended them by providing evidence that cell-associated activation may be taking place. C5b-9, B, and C3 antigens were observed as linear granular staining patterns within fibrous lacunae. The linear objects within the lacunae also stained with anti-SMC myosin antibodies, consistent with previous observations that SMC are embedded within fibrous lacunae in atherosclerotic lesions. Anti-C5b-9 antibodies used in this study recognize epitopes, which arise only after assembly of the native C5 through C9 proteins into the C5b-9 complex. Since C5b-9 assembly occurs after C3/C5 convertase formation, immunohistochemical localization of C5b-9 complexes indicates that convertases were formed in lesions. C3b generated by the C3 convertase is prevented from making additional convertases (hence amplifying the activation process) through the actions of DAF, CR1, membrane cofactor protein, and Factors H and I. In terms of prevalence, the present report would indicate that DAF is the major complement regulatory mechanism in lesions, followed next by Factor H and CR1. Two additional regulatory proteins not examined are the C4b-binding protein and membrane cofactor protein.
Fibrous cap region of atherosclerotic carotid artery. In the lower right-hand comer is the lipid-rich necrotic core, which exhibits some autofluorescence. A. C5b-9 antigen appears in a linear pattern on objects embedded in fibrous lacunae. B. Consecutive section of lesion area depicted in A stained for Factor B antigen. Linear patterns of fluorescence in areas corresponding to C5b-9 fluorescence suggest co-deposition of Factor B and C5b-9 on identical objects. x300

Figure 6. Fibrous cap region of atherosclerotic carotid artery. In the lower right-hand comer is the lipid-rich necrotic core, which exhibits some autofluorescence. A. C5b-9 antigen appears in a linear pattern on objects embedded in fibrous lacunae. B. Consecutive section of lesion area depicted in A stained for Factor B antigen. Linear patterns of fluorescence in areas corresponding to C5b-9 fluorescence suggest co-deposition of Factor B and C5b-9 on identical objects. x300
was observed immunohistochemically. Since C3 convertase formation is based on a molar balance between Factor H and Factor B for binding to C3b, our data suggests that complement inhibition would, in general, be favored over activation. Furthermore, properdin, which promotes C3 convertase formation and stabilization and hence amplification of C3 activation, was found to be scarce in lesions.

At first sight, it may appear anomalous that lesions contain what appears to be effective defense mechanisms against complement activation, yet also contain a large quantity of C5b-9 antigen. However, C5b-9 is an approximately one million dalton protein complex, which is relatively resistant to proteolytic enzymes. It is, therefore, likely to remain at its site of formation for a considerable period of time. Hence, the C5b-9 complexes in a lesion probably represent a long-term accumulation of this material.

The results of the present study demonstrate for the first time that complement regulatory proteins and receptors are present in human atherosclerotic plaques. Further, through immunohistochemical detection of C5b-9 complexes, we and others have shown that complement is also activated in atherosclerotic plaques. Complement activation may contribute to the initiation and progression of atherosclerosis by attracting leukocytes, by modulating leukocyte inflammatory functions, and by contributing to tissue damage. It was, therefore, important to determine whether mechanisms for down-regulating complement activation in the arterial wall were present. We demonstrated that both cellular and extracellular complement regulatory proteins are present in plaques, but not in normal arterial wall. This suggests that mechanisms for inhibition of complement activation are elicited during atherogenesis and supports our hypothesis that the complement system plays a role in the development of atherosclerosis.

Acknowledgments

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