Regional Accumulations of T Cells, Macrophages, and Smooth Muscle Cells in the Human Atherosclerotic Plaque

Lena Jonasson, Jan Holm, Omar Skalli, Göran Bondjers, and Göran K. Hansson

The cellular composition of human atherosclerotic plaques was analyzed by immunologic techniques. Plaques were removed from the internal carotid artery during surgery, and a panel of monoclonal antibodies was used to identify cell types. Macrophages stained by Anti-Leu-M3 were found throughout the plaque, particularly in the lipid core region, where 60% of the cells reacted with this antibody. T cells expressing the T3 antigen were most abundant in the fibrous cap, where they constituted 20% of the cell population. T cells were also isolated from the plaque and detected by a rosetting test; many of these T cells were activated, as indicated by the expression of HLA-DR. Other types of leukocytes were uncommon in the plaque. An antibody to the intermediate filament protein, desmin, was used as a marker for smooth muscle cells since some, but not all, vascular smooth muscle cells contain this protein. The desmin-positive cells were uncommon in the nonatherosclerotic intima but were more numerous in the plaque. In conclusion, atherosclerotic plaques are heterogeneous with respect to cellular composition. The smooth muscle cell dominates in the fibrous cap, which also contains many T cells; the lipid core is dominated by macrophages. We suggest that interactions between smooth muscle cells and blood-borne cells are important in the pathogenesis of atherosclerosis.

Methods

Antibodies

The characteristics of the antibodies used in the study are shown in Table 1. The cell-type specific mouse monoclonal antibodies, Anti-Leu-2a, Anti-Leu-3a + b, Anti-Leu-4, Anti-Leu-7, and Anti-Leu-M3, were purchased from Becton Dickinson, Mountain View, California. Dako-pan-B was obtained from Dako, Copenhageren, Danmark. Rabbit antivimentin was prepared by immunization of rabbits with vimentin that had been purified from bovine endothelial cells by preparative SDS electrophoresis. Rabbit antidesmin, raised against chicken gizzard desmin, was used as the affinity-purified antibodies. Biotinylated horse antimouse IgG and avidin-biotin-peroxidase complexes were purchased from Vector Lab, Burlingame, California. Rhodamine-conjugated swine antirabbit-IgG was obtained from Dako. Immunobeads coated with rabbit antihuman immunoglobulins were purchased from Bio-Rad Laboratories, Richmond, California.

Arterial Tissue

Atherosclerotic plaques were obtained from the internal carotid artery of 16 patients who were between 57 and 75 years old and who did not have any other systemic diseases. The patients were operated on because of transient ischemic attacks, and plaques were obtained during endarterectomy. Nonatherosclerotic arterial tissue was obtained from the aortic base during coronary bypass surgery (five patients, 53 to 69 years old), and from the uterine artery during hysterectomy (four patients, 26 to 48 years old). The operative procedures were done according to the hospital routines, and informed consent was obtained from all patients taking part in this study. The biopsies were immersed in ice-cold Hanks buffered salt solution (HBSS), transported to the laboratory, and were processed within 20 minutes from the time of excision.

Immunocytochemistry

The tissue samples were snap-frozen in n-hexane that had been chilled with liquid nitrogen. The 8 µm cryostat sections were fixed with 95% ethanol, were rinsed in phosphate-buffered saline (PBS, 150 mM NaCl, 20 mM phosphate buffer, pH 7.4) and were preincubated with 2% normal serum. They were then incubated with either mouse monoclonal or rabbit polyclonal antibodies, all diluted in PBS with 4% bovine serum albumin (Sigma, St. Louis, Missouri). After repeated rinsing with PBS, the sections that had been reacted with monoclonal antibodies were incubated in a similar fashion with biotinylated second-step antibodies. This was followed by incubation with 0.3% hydrogen peroxide in methanol to eliminate endogenous peroxidase activity. The sections were rinsed repeatedly and were incubated with the avidin-biotin-peroxidase complex. The peroxidase was visualized by incubation with diaminobenzidine (1 mg/ml) and hydrogen peroxide (0.01%) in PBS. The cells were counterstained with Mayer’s hemalum, stained with Mayer’s Hemalun, and finally mounted again. All antibodies were used at optimal dilutions determined by chessboard titrations. In control slides, the first-step antibody was omitted.

Quantitation of Positive Cells

The cells were counted at x 200 magnification (x 20 objective, x 10 eyepieces) in the following regions of the plaque: the intima adjacent to the plaque (Region I); the “shoulder region” in the periphery of the plaque (II); the fibrous cap (III); and the necrotic core region (IV). Region I was identified as the visual field of thickened intima immediately outside the edge of the plaque. Region II was defined as the field in the plaque immediately proximal to the edge. In Region III, the field at the “summit” of the plaque was counted, and in Region IV, the field directly below Field 3 and immediately under the border between the cap and core was counted. All immunoreactive, nucleated cells were counted in these fields, and the total number of cells was determined by counting all Htx-positive nuclei.

Histochemistry

Fresh cryostat sections were incubated for 40 minutes in a substrate solution for detection of alpha-naphthyl acetate esterase, as described. Then they were counterstained with Mayer’s hemalum. Ethanol-fixed cryostat sections were incubated with 1 mg/ml diaminobenzidine and 0.01% hydrogen peroxide for visualization of endogenous peroxidase activity. The positive cells were counted as described above.

Isolation of Cells

The isolation procedure was a modification of the method used by Haley et al. Parts of the plaques were immediately cut into small pieces with fine scissors, were washed twice with HBSS by low-speed centrifugation, and were digested for 60 minutes at 37°C in a shaking water bath, in 900 IU/ml collagenase (Cl. histolyticum type I, Sigma), 125 U/ml elastase (Sigma), 1.0 mg/ml soybean trypsin inhibitor (Sigma), and 5.0 mg/ml bovine serum albumin in calcium- and magnesium-free HBSS. The digested material was filtered through a 150 mesh nylon filter, and cells were harvested by low-speed centrifugation. Approximately 2 x 10^5 cells were obtained per gram of tissue. They were washed twice with HBSS and subjected to the receptor assays described below. All glassware used for these experiments was siliconized.
**Fc Receptor Assay**

A washed concentrate of sheep erythrocytes was incubated with antsheep erythrocytes (SBL, Stockholm, Sweden) for 60 minutes at room temperature.22 The coated erythrocytes were washed twice with PBS and suspended to a concentration of 1%. A mixture of 500 µl of a suspension of the isolated plaque cells (1 to 2 x 10^6 cells/ml), 200 µl fetal bovine serum (Flow Lab, Irvine, Scotland), and 10 drops of the erythrocyte suspension was centrifuged at 40 g for 5 minutes, and the loose pellet was incubated for 25 minutes at 37°C. The pellet was resuspended, and drops of cells were air-dried onto microscope slides and were fixed with ice-cold acetone. Rosetted cells and the total number of cells were counted in these droplets.

**Antibody-Mediated Phagocytosis**

The procedure was a modification of the technique used by Fowler et al.9 Isolated cells were incubated with coated erythrocytes as described for the Fc receptor assay. Incubation was for 60 minutes at 37°C, and the cells that had ingested erythrocytes were counted in the microscope.

**E Receptor Assay**

T cell-specific E receptors (sheep erythrocyte receptors) were detected with AET-(32-aminoethylisothiouronium-hydrobromide)-treated sheep erythrocytes at 10% in HBSS.23 Eight drops of this suspension were incubated with 500 µl of isolated plaque cells (1 to 2 x 10^6 cells/ml) and 200 µl fetal bovine serum, for 5 minutes at 37°C. The mixture was then centrifugated at 40 g for 5 minutes and was incubated as a loose pellet at 4°C overnight. The cells were resuspended to the initial volume, the nuclei were stained with Giemsa, and the total number of cells and the rosetted cells were counted.

**Cell Surface IgG Assay**

B cells were labeled for surface immunoglobulin by the use of Immunobeads. These are micron-sized hydrophilic polyacrylamide beads with covalently bound purified anti-human immunoglobulin antibodies.24 Isolated plaque cells were incubated in HBSS at 37°C for 30 minutes to remove adsorbed immunoglobulins. 100 µl of isolated cells (1 to 2 x 10^6 cells/ml) were then mixed with 50 µl Immunobeads. The mixture was centrifugated at 150 g for 30 minutes and incubated overnight at 4°C. The cells were resuspended and the nuclei were stained. Rosetted cells were counted using phase contrast microscopy.

**Results**

The general appearance of the plaque as it is shown in Figure 1 formed the basis for the analysis of the data. As illustrated, the plaque was subdivided into the intima surrounding the plaque (I), the "shoulder region" or periphery of the plaque, which is histologically a part of the fibrous cap (II), the fibrous cap on the central part of the lesion (III), and the lipid-rich core region (IV). This subdivision of the plaque is analogous to that used in our studies of experimental lesions in cholesterol-fed rabbits.17,18 It does not, however, take into account findings such as rupture or thrombosis. Therefore, no such areas were included in the analysis.
Table 1. Mouse Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Cell type</th>
<th>Clone</th>
<th>Antigen</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Leu-M3</td>
<td>Monocytes/macrophages</td>
<td>MOP9</td>
<td>NC</td>
<td>14</td>
</tr>
<tr>
<td>Anti-Leu-7</td>
<td>Large granular lymphocytes</td>
<td>HNK-1</td>
<td>NC</td>
<td>51</td>
</tr>
<tr>
<td>Anti-Leu-4</td>
<td>T-cells</td>
<td>SK7</td>
<td>T3</td>
<td>27</td>
</tr>
<tr>
<td>Anti-Leu-2a</td>
<td>T cytotoxic/suppressor cells</td>
<td>SK1</td>
<td>T8</td>
<td>25, 26, 27</td>
</tr>
<tr>
<td>Anti-Leu-3a+b</td>
<td>T helper/inducer cells</td>
<td>SK3+SK4</td>
<td>T4</td>
<td>25, 26, 27</td>
</tr>
<tr>
<td>Dako-pan-B</td>
<td>B cells</td>
<td>To15</td>
<td>NC</td>
<td>—</td>
</tr>
<tr>
<td>OKla1</td>
<td>DR+ cells</td>
<td></td>
<td>HLA-DR</td>
<td>33</td>
</tr>
</tbody>
</table>

NC = not characterized.

The cell density differed markedly between regions and was $117 \pm 8$ cells per mm$^2$ (mean ± se) in Region I, $203 \pm 11$ in Region II, $91 \pm 8$ in Region III, and $205 \pm 18$ in Region IV.

Serial sections of plaques were incubated with a battery of antibodies to identify specific cell types (Table 1). The monoclonal antibodies were directed against cell type-specific cell surface antigens, and the polyclonal ones against intermediate filament proteins.

Cells expressing the macrophage antigen Leu-M3 were most frequent in the necrotic core region of the plaque (Figures 2 to 4 A), where almost two-thirds of all cells were Leu-M3$^+$ (Table 2). Many of these cells contained cytoplasmic droplets stainable with oil red O (data not shown). Approximately one-fifth of the cells in other parts of the plaque were Leu-M3$^+$, and 8.6% were positive with this antibody in the surrounding intima (Table 2). The distribution of this monocyte-macrophage marker corresponded with that of cells positive for alpha-naphthyl acetate esterase (Figure 4). No Leu-M3$^+$ cells were found in the intima or media of nonatherosclerotic arteries.

Cells positive with the pan-T cell antibody Anti-Leu-4, which reacts with the T3 antigen, were predominantly found in the fibrous cap, where one-fifth of all cells were T3$^+$ (Figures 5 and 6). In contrast, few T3$^+$ cells were detected in the necrotic core or surrounding intima. Nonatherosclerotic arteries were also negative with this antibody.

T cells were subdivided into T4$^+$ and T8$^+$ subsets. The former antibody has been shown to bind to helper-inducer T cells, and the latter, to suppressor and cytotoxic T cells. Both types of T cells were detected in all regions of the plaques (Table 3), but there were significantly more T4$^+$ than T8$^+$ cells in the fibrous cap. The antibodies Anti-Leu-7 and Dako-pan-B, which recognize killer and natural killer cells and B cells, respectively, stained very few cells in the plaques (Table 2).

Figure 3. Leu-M3$^+$ cells (arrows) and Leu-M3$^-$ cells (arrowhead) in the necrotic core of the plaque (immunoperoxidase and Htx, $\times 400$, bar = 10 $\mu$m).

Figure 4. A. Part of the necrotic core region (nc) and the underlying media (m). Leu-M3 staining. Notice the high number of Leu-M3$^+$ cells with dark-stained cytoplasm around the amorphous, noncellular part of the core region (immunoperoxidase and Htx, $\times 110$, bar = 50 $\mu$m). B. Demonstration of alpha-naphthyl acetate esterase in a serial section showing the same area of the plaque as in A. The distribution of the enzyme corresponds to the one of the Leu-M3$^+$ cells ($\times 110$, bar = 50 $\mu$m).
Table 2. Cellular Composition of the Plaque

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Intima</th>
<th>Shoulder</th>
<th>Fibrous cap</th>
<th>Necrotic core</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophages</td>
<td>6.6 ± 1.5&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>18.2 ± 3.4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>23.9 ± 3.7&lt;sup&gt;e&lt;/sup&gt;</td>
<td>60.3 ± 5.1&lt;sup&gt;f,g&lt;/sup&gt;</td>
</tr>
<tr>
<td>T cells</td>
<td>7.7 ± 2.5&lt;sup&gt;g&lt;/sup&gt;</td>
<td>21.6 ± 3.2&lt;sup&gt;h&lt;/sup&gt;</td>
<td>17.5 ± 2.4&lt;sup&gt;i&lt;/sup&gt;</td>
<td>9.2 ± 2.3&lt;sup&gt;j&lt;/sup&gt;</td>
</tr>
<tr>
<td>NK/K cells</td>
<td>0.1 ± 0.1</td>
<td>0.4 ± 0.3</td>
<td>0.5 ± 0.3</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td>B cells</td>
<td>0.5 ± 0.4</td>
<td>0.6 ± 0.3</td>
<td>0.9 ± 0.4</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>0</td>
<td>0.1 ± 0.1</td>
<td>0.4 ± 0.2</td>
<td>0</td>
</tr>
<tr>
<td>Desmin&lt;sup&gt;+&lt;/sup&gt;</td>
<td>5.8 ± 0.7&lt;sup&gt;k,l&lt;/sup&gt;</td>
<td>20.7 ± 2.5&lt;sup&gt;m,n&lt;/sup&gt;</td>
<td>61.2 ± 2.1&lt;sup&gt;i,l,m&lt;/sup&gt;</td>
<td>28.5 ± 2.4&lt;sup&gt;i,n,o&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are % of total number of cells, mean ± SE. Values having the same superscript are significantly different (p < 0.05).

Figure 5. T<sup>+</sup> cells are seen as cells with dark-stained cytoplasm primarily in the "shoulder" (sh) and in the fibrous cap (fc). Few positive cells are seen in the surrounding intima (in) and in the necrotic core region (nc). The larger dark spots in the core region are calcium deposits. Part of the media (m) is seen (Immunoperoxidase and Htx, × 30, bar = 100 μm).

Figure 6. T<sup>+</sup> cells (arrows) and T<sup>+</sup> cells (arrowhead) in the "shoulder" region (Immunoperoxidase and Htx, × 255, bar = 20 μm).

Granulocytes were identified by histochemical staining for endogenous peroxidase in combination with characteristic nuclear structure. They usually appeared subendothelially in the cap and shoulder regions and in low frequencies (Table 2).

We did not have access to any marker for the entire smooth muscle cell population, but we used antidesmin to identify smooth muscle cells expressing this muscle-specific intermediate filament protein. Desmin-positive cells were rare in the surrounding intima, but increased in the shoulder region (Table 2). Both in the fibrous cap and in the necrotic core, all nonleukocytic cells appeared to be desmin-positive. The frequency of desmin-positive cells was only 7% of the nonleukocytic cells in the surrounding intima, but was much higher in the plaque. Of the nonleukocytic cells, 35% were desmin<sup>+</sup> in the shoulder region and 100% were desmin<sup>+</sup> in the core region and in the central fibrous cap. Antivimentin stained 98% of the cells in the plaque and was detected both in leukocytic cells and in cells assumed to be smooth muscle cells.
The intermediate filament protein, desmin, appears only in muscle cells, B cells, granulocytes, and certain T and killer cells. Approximately 23% of all isolated cells showed a capacity for antibody-mediated phagocytosis, which is characteristic of monocytes, macrophages, and granulocytes. No B cells were detected by immunobeads reacting with their cell surface IgG (data not shown). E receptors characteristic for T cells were detected on 5% of the cells. Approximately 60% of E receptor-positive cells expressed the class II transplantation antigen HLA-DR, which was detected by a monoclonal antibody. In vitro, HLA-DR appears on T cells after activation by antigen or lectins, and our data therefore suggest that many of the T cells in the plaques were in an activated state.

Many uncertainties remain about the composition of the human atherosclerotic plaque. One reason is that morphologic techniques alone cannot be used to identify the cells in the plaque with any certainty. Even at the electron microscopic level, discrimination between large lymphocytes, macrophages, and even some smooth muscle cells is very difficult. We have therefore used an alternative approach and applied the monoclonal antibody technique to identify cells in the plaques. The rationale for this approach is that it is possible to prepare monoclonal antibodies against cell surface antigens that appear on the surface of only one specific cell type. This has turned out to be a fruitful strategy in studies of cell differentiation and cellular interactions in the immune system.

In the present study, we have applied well-defined monoclonal antibodies to leukocytes for cell-type identification in sections of human atherosclerotic plaques, assuming that these cells would maintain their cell-surface antigens in the tissue. Our data suggest that this is indeed the case. For instance, the distribution of Leu-M3 + cells corresponds to that of the histochemical macrophage marker, alpha-naphthyl acetate esterase; also, the numbers of different subpopulations of T cells (T4 + and T8 + cells) add up to approximately the same number of cells as that stained by the pan-T cell marker T3. There was, unfortunately, no antibody or other marker available to us which would recognize the entire smooth muscle cell population. The intermediate filament protein, desmin, appears only in muscle cells, and all plaque cells that contain desmin can therefore be identified as smooth muscle cells. However, many vascular smooth muscle cells lack desmin and have intermediate filaments formed only by vimentin. We were unable to recognize such desmin +, vimentin + smooth muscle cells, since leukocytes also contain vimentin.

The three-dimensional shape of the different types of cells creates another problem in the interpretation of the data. Fusiform cells will appear in several sections, and there is a risk that the frequency of such cells is overestimated, and the frequency of round cells is underestimated. We have reduced this bias by counting only cells whose nuclei are seen in the section. We may, however, still have overestimated the frequency of smooth muscle cells, since their nuclei are also more fusiform than those of leukocytes. One should be aware of these problems when interpreting the present results.

Our data are compatible with the theory that the majority of cells in the fibrous cap are derived from smooth muscle cells, since they do not react with any of the markers for macrophages or leukocytes. Furthermore, a substantial proportion of these cells contained the muscle-specific intermediate filament protein desmin, and ultrastructural studies in other laboratories have shown that many of the cells in these regions contain myofilaments and dense bodies.

The frequency of desmin-positive cells was only 6% in the intima surrounding the plaque, but was 21% in the shoulder region and 58% in the fibrous cap. The data from the fibrous cap and core regions suggest that virtually all smooth muscle cells in this region contain desmin. Gabbanii et al. have shown that the smooth muscle cells that proliferate in the intima after a balloon injury are predominantly vimentin +, desmin -, while desmin + cells are frequent in a long-standing intimal lesion in which proliferation is low. If this is also the case in humans, our data could suggest that proliferating, desmin - cells appear mainly in the surrounding intima and shoulder region, whereas the central fibrous cap contains mainly stationary, desmin + cells.

The data presented in this paper indicate that a large proportion of the cells of the carotid plaque are derived from the blood. These cells have characteristic distributions in the different regions of the plaque. Leu-M3 + macrophages constitute almost two-thirds of the cells in the core region. A fairly large proportion (approximately 25%) of the cells in the fibrous cap and the shoulder region are also positive for this monocyte-macrophage marker. Similarly, 32% of the cells isolated from the plaques had Fc receptors, which are present on macrophages and some leukocytes, and 23% were capable of antibody-mediated phagocytosis. The detection of macrophages in plaques by these techniques agrees with recent studies using other monoclonal antibodies.

It is likely that macrophages enter the plaque as monocytes, and entry of monocytes into early lesions has been observed in several experimental models. In the cholesterol-fed rabbit, monocytes preferentially stick to areas where there is endothelial cell injury, and we have shown that this is dependent on an interaction between the Fc receptor of the monocyte and IgG deposited on cytoskeletal, intermediate filaments of the injured cell. Circumstantial evidence from several laboratories suggests that macrophages are involved in the elimination of cholesterol from plaques, and we have recently observed that macrophage-derived foam cells of human plaques express the apolipoprotein E gene (G Bondjers et
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Jonasson et al.

Acknowledgments

We thank Tore Schersten, Kent Lundholm, and Fredrik Lundgren for providing surgical material and Elisabeth Lagerstedt for her skilled technical assistance.

References


al., unpublished data). Finally, macrophages produce growth factors for mesenchymal cells and for T cells, which could be important for the further progression of the lesion.41–43

The most surprising finding in the plaque was the high frequency of T lymphocytes, which were virtually absent from normal human arteries. They were particularly common in the fibrous cap where one-fifth of all cells expressed the T cell receptor-associated protein T3.

The conclusion that T cells are present in the plaque was confirmed by an independent test. Of the cells isolated from the plaque after collagenase digestion, 5% expressed the E receptor, which is a unique T cell function.23 The proportion of E cells in the isolates was lower than one might have expected from the staining data with antibodies to T3 on sections, but this may be due to enrichment of other cell types during the isolation procedure, or to destruction of some E receptors during enzymatic digestion. The mechanisms for recruitment of T cells to plaques are unclear. Soluble mediators produced by other cell types could play a role; in particular, Interleukin-1 produced by macrophages has been shown to attract lymphocytes.42 However, Interleukin-1 is reportedly at least as effective as a B cell chemoattractant as it is for T cells.44 The selective accumulation of T cells observed in the plaque must therefore be due either to a selective recruitment of T cells by another chemotactic mechanism, or to a selective trapping of T cells once they are in the plaque. The latter could be caused by tissue antigens to which clonal T cells react. Such a stimulation of specific T cells by antigens would lead to an activation and a proliferation of the T cells; a substantial proportion of the T cells in the plaque were indeed activated, as reflected in their expression of HLA-DR.

The products of activated lymphocytes may induce a differentiation or phenotypic modification of many cells. The best known example of this is the ability of gamma interferon, which is a product of activated T cells, to induce the expression of class II MHC antigens (in humans, HLA-DR, DQ, and DP) on target cells, which may then serve as antigen-presenting cells.45 We have recently reported46 that smooth muscle cells in atherosclerotic plaques (but not in normal arteries) express HLA-DR. Taken together with the present observation of a high frequency of activated T cells in the plaque, this suggests that interferon released from such cells can induce a phenotypic change in nearby smooth muscle cells, which is characterized by expression of HLA-DR.

Lymphocytes may also modulate local lipoprotein metabolism and cell proliferation. Conditioned media from activated lymphocytes increase LDL uptake by fibroblasts,47 but inhibit uptake of both native and malondialdehyde-modified LDL by macrophages.48 This makes it possible that lymphokines are involved in the control of cellular response to LDL influx in the developing plaque. Similarly, a lymphokine released by activated T cells induces proliferation of quiescent mesenchymal cells,49 and this could be another mechanism for T cell modulation of vascular cell reactions.

In summary, this study of human atherosclerotic plaques has shown that these lesions are heterogeneous with respect to cellular composition. Macrophages, T lymphocytes, and different types of smooth muscle cells appear in different numbers in different regions of the plaque. It seems reasonable to suggest that interactions between these cell types are important for the progression of the disease.
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Index Terms: atherosclerosis • desmin • immunocytochemistry • monoclonal antibodies • macrophages • smooth muscle cells • T lymphocytes
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doi: 10.1161/01.ATV.6.2.131

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