Electron Microscopic Studies of Phenotypic Modulation of Smooth Muscle Cells in Coronary Arteries of Patients With Unstable Angina Pectoris and Postangioplasty Restenosis

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**Background** Proliferation and matrix protein secretion of coronary smooth muscle cells (SMCs) have been suggested as one of the mechanisms responsible for the development of postangioplasty restenosis and an alternative cause of unstable angina. Phenotypic modulation of SMCs may produce a pool of cells potentially responsive to growth stimulation that can synthesize abundant extracellular matrix. This study tested the hypothesis that phenotypic modulation of SMCs occurred during the evolution of postangioplasty restenosis and unstable angina.

**Methods and Results** The SMCs of coronary atherectomy specimens from 24 patients were identified under electron microscope. Volume fractions of synthetic organelles (VFSOs) and other features related to phenotypic modulation of SMCs were measured. The results showed that the VFSO in SMCs from 5 patients with unstable angina (group 2) resembled those from 9 patients with postangioplasty restenosis (group 3; 0.42±0.13 versus 0.36±0.10; *P*=NS), and both were significantly higher than those from 6 patients with stable angina (group 1; 0.21±0.11). Four patients with restenosis lesions who underwent angioplasty >6 months ago (group 4) also had a low VFSO in SMCs (0.19±0.05). This value was significantly less than those in groups 2 and 3 (*P*<0.05) but similar to that in group 1.

**Conclusions** The coronary lesions from patients with unstable angina resembled those from patients with postangioplasty restenosis in terms of the phenotypic modulation and VFSO in SMCs. Our findings therefore suggest that after phenotypic modulation, the SMCs may become responsive to growth stimulation, with an ability to massively proliferate and synthesize abundant extracellular matrix. These processes may lead to plaque expansion and eventually to the development of unstable angina and restenosis. (*Circulation. 1997;95:1169-1175.)*

**Key Words** smooth muscle • angina • angioplasty • restenosis

Restenosis after successful percutaneous transluminal coronary angioplasty is the major limitation of the procedure. The pathophysiology of restenosis is complex and incompletely understood. It is mediated in part by an uncontrolled proliferation and extracellular matrix synthesis by modified smooth muscle cells (SMCs), although arterial remodeling as the potential contributing process has recently gained increased attention. 8

SMCs are also suggested to play a role in the pathogenesis of unstable angina. It has long been believed that coronary plaque disruption and subsequent platelet aggregation and thrombosis are the most important mechanisms responsible for the transformation of asymptomatic stable coronary lesions into symptomatic unstable lesions. However, studies have postulated that SMC proliferation may lead to gradual plaque expansion and thus to luminal narrowing and unstable angina. 9

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It has been suggested that a phenotypic modulation of SMCs occurs before SMC division. 6,7 There are two different phenotypes of SMCs. 8 During most of the fetal and early postnatal periods, the medial layer of the artery is made up of SMCs of the synthetic phenotype, characterized by extensive rough endoplasmic reticulum, a prominent Golgi apparatus, and only a few myofilaments. They proliferate and secrete extracellular matrix. During development, the arterial SMCs shift from a synthetic to contractile phenotype. The cell in the contractile phenotype is quiescent with numerous myofilaments, and it provides both vasomotion and structural support to the vessel. However, studies in animal models have shown that the SMCs are able to shift back to a synthetic phenotype during the process of atherogenesis 9,10 and intimal thickening after endothelial injury. 11

There has been no quantitative study on the morphologic change of SMCs in the evolution of postangioplasty restenosis and unstable angina in human coronary arteries. To determine the role of SMC proliferation in terms of phenotypic modulation in the restenosis process and in the development of unstable angina pectoris, the phenotype of SMCs was examined morphometrically by use of directional coronary atherectomy specimens with a transmission electron microscope in patients with stable angina, unstable angina, and postangioplasty restenosis.
Patient Population

Coronary atherectomy specimens were obtained from 24 patients with the Simpson AtheroCath (Devices for Vascular Intervention). The patients had been selected for atherectomy rather than conventional balloon angioplasty on the basis of the presence of a localized stenosis in the proximal or middle portion of a vessel with a reference segment diameter of \( \approx 2.5 \) mm. During atherectomy, multiple cuts (generally 10 to 15) were performed with various orientations of the window. The atherectomy specimens of the 24 patients were subdivided into four groups.

Group 1 included six primary lesions from patients with chronic stable angina. Group 2 was made up of five primary lesions from patients with unstable angina. Group 3 consisted of nine restenosis lesions; the time interval from study to prior angioplasty was <6 months for each. Group 4 included four restenosis lesions, with an interval from the previous procedure of >6 months. Unstable angina was defined as one of the three clinical syndromes: angina pectoris at rest, crescendo angina, or angina pectoris of new onset. This study was approved by the Human Research Committee of Veterans General Hospital-Taipei (Taiwan).

Histopathological Study

Part of the DCA samples were fixed at the time of procedure in 10% buffered formalin, dehydrated in graded series of alcohol, and embedded in paraffin block. Serial sections were stained with hematoxylin and eosin. The presence of a rim of atheromatous material (macroscopically yellow) or superficial thrombi (gray or red) helped us to decide how to orient the samples. When these features were absent, samples were embedded according to their major axes. The specimens were analyzed for the presence or absence of media (medial tissue was identified on the basis of parallel arrangement of SMCs, embedded in collagen, and frequently associated with fragments of the elastic laminae) and thrombus and hemorrhage.

Transmission Electron Microscopy

Part of the atherectomy specimens were placed in 2.5% glutaraldehyde and 2% paraformaldehyde in 0.1 M cacodylate buffer, pH 7.4, for 2 hours. These samples were then washed several times with the same buffer, postfixed with 1.5% osmium tetroxide for 2 hours, and dehydrated in graded alcohol. The tissue was then embedded in Epon 812 in small coffin molds. The orientation of the samples was determined as described previously. Thick sections from randomly selected blocks were cut and stained with methylene blue for light microscopy. Thin sections were cut with a diamond knife on a Reichter ultramicrotome; the sections were mounted on Formvar single-hole grids or 150-mesh grids, stained with uranyl acetate and lead citrate, and then examined at 80 kV under electron microscope (JEOL JEM 2000EXII).

Analysis of Cell Type

The morphological criteria used for recognition of SMCs were the presence of basal lamina, plasmalemmal vesicles, and myofilament bundles with associated dense bodies. Only those cell profiles of sufficient size to be characterized as SMCs by those criteria were counted. The presence or absence of inflammatory cells and red blood cells was also noted.

Morphometry of SMCs

The morphometric methods used for determining the volume fractions of synthetic organelles of SMCs were described in detail previously. A primary magnification of \( \times 3600 \) or \( \times 4000 \) was used. Each negative was enlarged to a final magnification of \( \times 13800 \).

Double quadratic test lattices with a spacing of 8 and 16 mm were used. These lattices had a total of 682 points. The ratio of coarse points to fine points was 1:4. The lattices were placed over the prints, and the lattice intersections were used for point-counting volumetry.

For each lesion studied, 15 to 26 photographs of SMCs were taken and calculated for volume fractions of synthetic organelles of SMCs separately. The means and SDs of the volume fraction of synthetic organelles for each lesion were calculated.

Other features related to phenotype modulation of SMCs were also observed. These included (1) nuclear changes such as volume ratio of nucleus to cytoplasm and that of nuclear heterochromatin to euchromatin (they were also quantified by double quadratic test lattice as described above), binucleation, and expansion in size of the nucleus; (2) a change in the amount of collagen, which was semiquantitatively in fixed areas surrounding each SMC; (3) the presence or absence of apoptosis (dropping off and fragmentation of the cytoplasm and nucleus); and (4) a change in cell shape such as pseudopod protrusion.

Statistical Analysis

All data were expressed as mean±SD. The difference in mean values among different groups and patients was analyzed by one-way ANOVA with post-hoc test. Scheffe’s test was applied to adjust for multiple comparison. A value of \( P<0.05 \) was considered statistically significant.

Results

Baseline Characteristics

Of the 24 patients in the study, 22 were men and 2 were women; their mean age was 63.0±7.5 years (range, 41 to 74 years). Directional coronary atherectomy was performed in 11 patients for primary lesions and in 13 patients with postangioplasty restenosis. Table 1 summarizes the

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical Characteristics</th>
<th>1 (n=6)</th>
<th>2 (n=5)</th>
<th>3 (n=9)</th>
<th>4 (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>6/0</td>
<td>6/1</td>
<td>8/1</td>
<td>4/0</td>
<td></td>
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<tr>
<td>Age (mean±SD), yr</td>
<td>65.3±5.5</td>
<td>63.0±8.7</td>
<td>61.2±9.1</td>
<td>64.5±2.1</td>
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<tr>
<td>Prior myocardial infarction, %</td>
<td>16.6</td>
<td>20.0</td>
<td>22.2</td>
<td>25.0</td>
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</tr>
<tr>
<td>Current smokers, %</td>
<td>50.0</td>
<td>86.0</td>
<td>44.4</td>
<td>50.0</td>
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<tr>
<td>Diabetes mellitus, %</td>
<td>0</td>
<td>0</td>
<td>11.1</td>
<td>25.0</td>
<td></td>
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<tr>
<td>Hb concentration, %</td>
<td>50.0</td>
<td>40.0</td>
<td>33.3</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>0/6</td>
<td>5/6</td>
<td>3/9</td>
<td>0/4</td>
<td></td>
</tr>
<tr>
<td>Systemic thrombolysis</td>
<td>0/6</td>
<td>1/5</td>
<td>0/9</td>
<td>0/4</td>
<td></td>
</tr>
<tr>
<td>Target vessels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>5</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>RCA</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
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</table>

LAD indicates left anterior descending artery; LCX, left circumflex artery; and RCA, right coronary artery. Group 1 consisted of primary lesions from patients with stable angina; group 2, primary lesions from patients with unstable angina; group 3, restenosis lesions, and the interval from the time of the study to the previous angioplasty was <6 months; and group 4, restenosis lesions, and the interval from the time of the study to the previous angioplasty was >6 months.

TABLE 1. Clinical Characteristics of the 24 Patients Studied
TABLE 2. Incidence of Coronary Thrombosis and the Presence of Vessel Media Detected by Histopathological Analysis of Directional Coronary Atherectomy Samples

<table>
<thead>
<tr>
<th>Findings</th>
<th>Group 1 (n=6)</th>
<th>Group 2 (n=5)</th>
<th>Group 3 (n=9)</th>
<th>Group 4 (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus, n (%)</td>
<td>1 (17)</td>
<td>3 (60)</td>
<td>2 (22)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Presence of media, n (%)</td>
<td>1 (17)</td>
<td>2 (22)</td>
<td>3 (33)</td>
<td>1 (25)</td>
</tr>
</tbody>
</table>

demographic and angiographic data for the subgroups. The mean time from atherectomy to prior procedure was 4.3 ± 1.5 months (range, 1 to 5.5 months) in patients from group 3. In patients from group 4, the mean time from atherectomy to previous angioplasty was 10.4 ± 6.4 months (range, 6.5 to 20 months).

Histopathological Findings

Table 2 summarizes the histological findings in the four groups of patients. Thrombus was present in 17%, 60%, 22%, and 25% of patients in groups 1, 2, 3, and 4, respectively.

Morphometric Analysis

Table 3 gives the quantitative results of the volume fractions of synthetic organelles in SMCs of the 24 patients in the four different groups.

In group 1, most of the SMCs were spindle shaped with few pseudopod protrusions. A few round cells were also observed. The cytoplasm of most cells was predominantly occupied by myofilaments. The organelles involved with biosynthesis were located in the perinuclear region and constituted only a minor portion of the cytoplasmic volume. The mean volume fraction of synthetic organelles in the SMCs of the whole group was 0.21 ± 0.11. In addition, their nuclei were small (mean volume ratio of nucleus to cytoplasm, 0.25 ± 0.06) and contained a higher ratio of heterochromatin (mean volume ratio of heterochromatin to euchromatin, 2.94 ± 1.18; Fig 1). Nucleoli were rarely found, and few SMCs had binucleation. But the SMCs obtained from patient 4 contained abundant synthetic organelles, and the volume fraction of synthetic organelles was 0.38 ± 0.11. The nuclei of the SMCs of this patient were also bigger and more euchromatic. Few inflammatory cells or red blood cells were observed in this group except in specimens from patient 4. There were small to moderate amounts of collagen near the SMCs.

In group 2, almost all the cells were spindle-shaped with multiple pseudopod protrusions. They contained abundant synthetic organelles and only small peripheral bundles of myofilaments (Fig 2). The mean volume fraction of this group was 0.42 ± 0.13. The highest value was noted in patient 3 (0.62 ± 0.15), who had sustained an acute myocardial infarction 2 weeks before coronary atherectomy and had persistent angina at rest before the procedure. The mean volume fraction of synthetic organelles in the SMCs of group 2 was approximately twice the value of the cells in group 1 (P<.05). Their nuclei were bigger than those of group 1 (mean volume ratio of nucleus to cytoplasm, 0.44 ± 0.04) and contained a higher ratio of euchromatin (mean volume ratio of heterochromatin to euchromatin, 0.91 ± 0.25). They also had more nucleoli (n=3±1) of expanded size and more binucleation than those of group 1.

TABLE 3. Volume Fractions of Synthetic Organelles in Smooth Muscle Cells of 24 Patients in Four Different Groups

<table>
<thead>
<tr>
<th>Volume Fraction of Synthetic Organelles</th>
<th>Patient No.</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.19±0.07</td>
<td>0.29±0.12</td>
<td>0.30±0.14</td>
<td>0.16±0.05</td>
<td></td>
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<tr>
<td>2</td>
<td>0.28±0.11</td>
<td>0.39±0.13</td>
<td>0.22±0.15</td>
<td>0.25±0.10</td>
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<tr>
<td>3</td>
<td>0.18±0.10</td>
<td>0.62±0.15</td>
<td>0.35±0.12</td>
<td>0.21±0.11</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.38±0.11</td>
<td>0.32±0.14</td>
<td>0.40±0.07</td>
<td>0.14±0.07</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.10±0.06</td>
<td>0.48±0.14</td>
<td>0.32±0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.12±0.08</td>
<td>0.49±0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.33±0.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.28±0.07</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>9</td>
<td>0.43±0.17</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean±SD</td>
<td>0.21±0.11</td>
<td>0.42±0.13</td>
<td>0.36±0.10</td>
<td>0.19±0.05</td>
<td></td>
</tr>
</tbody>
</table>

The numbers in parentheses are the numbers of smooth muscle cells studied.

Fig 1. A smooth muscle cell taken from a patient in group 1 with primary lesions and chronic stable angina. The cell shows typical features of the contractile phenotype. The cytoplasm was predominantly occupied by myofilaments (mf) anchored to dense bodies (arrows). Magnification x14,000.
Numerous inflammatory cells and red blood cells were observed in the specimens from three patients. A few SMCs with dropping off and fragmentation of the cytoplasm and nucleus, showing ultrastructural characteristics of apoptosis, were found in patient 3. There were moderate amounts of collagen near the SMCs.

In group 3, most of the SMCs were spindle-shaped with multiple pseudopod protrusions. They displayed a range of ultrastructure. Most of the cells contained abundant synthetic organelles and relatively fewer myofilaments (Fig 3). Other cells, however, were observed to have fewer synthetic organelles. The mean volume fraction of synthetic organelles of this group was 0.36±0.10. This value was significantly higher than that of the cells in group 1 ($P<.05$) but was slightly lower than that of group 2 ($P=NS$). The values of volume fractions of synthetic organelles in smooth muscle cells, however, had no correlation with the time interval from the tissue obtained by atherectomy to previous angioplasty. Furthermore, their nuclei were also bigger than those of group 1 (mean volume ratio of nucleus to cytoplasm, 0.37±0.06) and contained a higher ratio of euchromatin (mean volume ratio

**Fig 2.** Smooth muscle cells from patients in group 2 with primary lesions and unstable angina. A, The cell shows the characteristics of synthetic phenotypes with abundant synthetic organelles and few myofilaments. B, A higher magnification of a smooth muscle cell shows that the cytoplasm contains synthetic organelles with rough endoplasmic reticulum (arrowheads), Golgi complex (arrow), and mitochondria (m). C, A part of a smooth muscle cell shows that the cytoplasm contains a lot of rough endoplasmic reticulum (arrowheads), mitochondria (arrows), and lipid droplets (L). Magnification ×7200 (A), ×14,400 (B), and ×6600 (C).

**Fig 3.** A smooth muscle cell from a patient in group 3 with restenotic lesions obtained within 6 months after angioplasty. The cell shows a synthetic phenotype with a high volume fraction of synthetic organelles. Magnification ×8000.
of heterochromatin to euchromatin, 1.69±1.25). They also had more nucleoli (n=2±1) of expanded size and more binucleation than those of group 1. Inflammatory cells and red blood cells were observed in the specimens from three patients. No apoptosis was found. There were moderate to large amounts of collagen near the SMCs.

In group 4, most of the SMCs were spindle-shaped with few pseudopod protrusions. A few round cells were also observed. Almost all the cells had ultrastructural characteristics similar to the cells in group 1 (Fig 4), reflected by the low volume fraction of synthetic organelles (0.19±0.05). The value was significantly lower than those of the cells in groups 2 and 3 (P<.05) but similar to that of the cells in group 1. Their nuclei were small (mean volume ratio of nucleus to cytoplasm, 0.23±0.03) and contained a higher ratio of heterochromatin (mean volume ratio of heterochromatin to euchromatin, 3.53±1.57), similar to those of group 1. Nucleoli were sparse, and few SMCs had binucleation. Few inflammatory cells and red blood cells were observed. There were small amounts of collagen near the SMCs.

Fig 5 shows the mean values of volume fractions of synthetic organelles and the volume ratios of nucleus to cytoplasm and of nuclear heterochromatin to euchromatin in SMCs from the four different groups.

Discussion

The present study characterized phenotypic features of SMCs by quantitative morphological analysis under transmission electron microscope in human coronary arteries in different clinical settings. The results indicated that after balloon injury, the SMCs of coronary artery undergo significant changes in ultrastructure. Within 6 months of angioplasty, the volume fraction of synthetic organelles in SMCs of restenotic lesions was approximately twice that of the primary lesions, and their nuclei became bigger and more euchromatic. More than 6 months after angioplasty, the volume fractions of synthetic organelles in the SMCs decreased toward the level of primary lesions, and their nuclei became smaller and more heterochromatic, suggesting that a subsequent decline in proliferation and reversion of phenotype may occur with time. Our observations on coronary atherectomy materials indicated that the phenotypic features of SMCs in group 3 and 4 patients were similar to those during the evolution of experimental intimal thickening after balloon catheter injury in rat carotid artery.11 In experimental lesions, it has been generally accepted that SMCs become redifferentiated and contractile with time after balloon injury. This study also demonstrated that even in primary lesions, a phenotypic modulation with a sharp increase in the amount of synthetic organelles and the nuclear changes similar to restenosis lesions might be observed in SMCs from patients with unstable angina.

The cytoplasm of most SMCs from our group 1 patients was predominantly occupied by myofilaments, and few synthetic organelles were present. But there was one patient in group 1, whose SMCs contained abundant synthetic organelles with a high value of volume fraction of synthetic organelles. This result indicated that native coronary stenotic lesions do not consist exclusively of quiescent atherosclerotic plaque. Intimal proliferation was observed previously in restenotic lesions after a prior intervention, but the finding of intimal hyperplasia in atherectomy specimens from primary lesions has also been reported. Previous histological findings have shown that although >75% of the atherectomy samples from primary lesions consisted of atherosclerotic plaques, 22% to 42% of the primary lesions also contained intimal proliferative tissue.

Previous studies designed to investigate the mechanisms responsible for the development of unstable angina have concluded that the clinical syndrome is caused by plaque rupture, hemorrhage, and thrombus formation.16-18 In this study, patients with unstable angina have SMCs of a highly synthetic phenotype, and this observation is consistent with the histological findings reported by other studies.4,5 Moreover, the lesions resembled restenotic lesions in regard to SMC abundance. Thus, it has been hypothesized that in a subset of patients with unstable angina, hemorrhage into a plaque, minor fibrous cap tear and dissection, or other mitogenic stimuli might lead to the expression of multiple growth factors, in turn initiating a cascade of events in which the dominant component is SMC proliferation. The migration of SMCs from the underlying media into the plaque and the synthesis and secretion of extracellular matrix by SMCs lead to plaque expansion and thus to luminal narrowing and unstable angina. A study with intracoronary angioscopy has demonstrated that plaque rupture and thrombosis were present in 68% of unstable angina patients.19 These findings were similar to those observed in our study.

Because the morphological analysis used in the present study yielded an estimate of the average phenotype of the SMCs, the results tend to somewhat obscure the observa-
tion that cells in the neointima actually showed a range of ultrastructural characteristics. Although most cells of restenotic lesions obtained within 6 months of angioplasty may appear to have a synthetic phenotype, other cells with a higher content of myofilaments might be present. This range of phenotype expression may be important because different "subpopulations" of SMCs may have different proliferative potentials.

Some studies of postangioplasty restenosis at necropsy have shown only atherosclerotic plaques, with no morphological evidence of intimal hyperplasia. A histological study of atherectomy tissue from restenotic lesions also demonstrated that atherosclerotic plaque alone without associated intimal proliferative tissue was observed in 14% to 17% of patients. Possible explanations for restenosis in this subgroup of patients include elastic recoil of over-stretched vessel walls of eccentric atherosclerotic lesions, technically inadequate balloon dilatation, or tissue sampling error. These may account in part for the lack of success to date in clinical trials aimed at inhibiting restenosis by reducing SMC proliferation.

**Study Limitations**

The number of patients in each group is rather small in this study. Also, a sampling error in our specimens seems possible. Because the procedure of atherectomy entails circumferential rotation of the cutting edge, the intima of the normal vessel wall of eccentric atherosclerotic lesions may be retrieved. Besides, it is difficult to orient some small atherectomy specimens, so the possibility of the presence of medial cells within our specimens could not be avoided. Finally, a study using an electron microscope like this can examine only a small portion of the specimens; therefore, interpretation of the findings should be done cautiously. Verification of our data with other techniques is important.

**Conclusions**

This study suggests that a phenotypic modulation of SMCs occurs in the human coronary artery during the development of postangioplasty restenosis. A similar sequence of events may also be important in the pathogenesis of unstable angina. A reversion of phenotype may happen 6 months after angioplasty. These changes in SMCs from contractile to synthetic phenotype may be an important step in the initiation of SMC proliferation. A change of phenotype may produce a pool of SMCs potentially responsive to growth stimulation, with an altered ability to synthesize abundant extracellular matrix, and expansion of original plaque, eventually leading to the development of unstable angina and restenosis.

**Acknowledgments**

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