Proliferation in Primary and Restenotic Coronary Atherectomy Tissue
Implications for Antiproliferative Therapy


On the basis of animal models of arterial injury, smooth muscle cell proliferation has been posited as a dominant event in restenosis. Unfortunately, little is known about this proliferation in the human restenotic lesion. The purpose of this study was to determine the extent and time course of proliferation in primary and restenotic coronary atherectomy-derived tissue. Primary (n=118) and restenotic (n=100) coronary atherectomy specimens were obtained from 211 nonconsecutive patients. Immunocytochemistry for the proliferating cell nuclear antigen (PCNA) was used to gauge proliferation in the atherectomy specimens. The identity of PCNA-positive cells was then determined using immunohistochemical cell-specific markers. Eighty-two percent of primary specimens and 74% of restenotic specimens had no evidence of PCNA labeling. The majority of the remaining specimens had only a modest number of PCNA-positive cells per slide (typically <50 cells per slide). In the restenotic specimens, PCNA labeling was detected over a wide time interval after the initial procedure (eg, 1 to 390 days), with no obvious proliferative peak. Cell-specific immunohistochemical markers identified primary and restenotic PCNA-positive cells as smooth muscle cells, macrophages, and endothelial cells. In conclusion, the findings were as follows: (1) Proliferation in primary and restenotic coronary atherectomy specimens, as indicated by PCNA labeling, occurs infrequently and at low levels. (2) The response to injury in existing animal models of angioplasty may follow a very different course of events from the clinical reality in human atherosclerotic coronary arteries and may help explain why current approaches to restenosis therapy have been ineffective. (Circulation Research 1993;73:223-231)

KEY WORDS • atherosclerosis • restenosis • coronary atherectomy • proliferation

The therapeutic potential of interventional cardiology is limited by the high proportion of patients who develop postprocedural restenosis. The mechanisms leading to restenosis remain unclear. Arterial recoil, accelerated progression of the underlying atherosclerotic lesion, overproduction of extracellular matrix, thrombus formation, and smooth muscle cell proliferation have been proposed as the critical processes leading to restenosis.1 Intimal hyperplasia due to smooth muscle cell proliferation is most commonly cited as the dominant cellular event in the restenotic process.2-5 Drugs that inhibit smooth muscle cell hyperplasia following angioplasty in experimental animals have been administered to patients with the hope of preventing restenosis. Although in some clinical trials the dose of the study drug differed from that used in the animal experiments, to date all drugs that have been clinically tested appear to be unsuccessful in preventing restenosis, at least according to angiographic end points that measure only loss of lumen diameter.6,7 The limited utility of animal models suggests either that the biology of restenosis is very different in animals compared with human atherosclerotic vessels or that restenosis is due to processes other than the intimal hyperplasia that is usually studied in animal models.

The most extensively studied animal model involves balloon injury to the rat carotid artery.8 The kinetics of this model are very well characterized. Unlike a human coronary artery, the normal rat carotid artery lacks the innermost arterial layer or intima. Within the first 48 to 72 hours following balloon angioplasty, there is a wave of smooth muscle cell proliferation involving from 10% to over 50% of the medial smooth muscle cells. Medial proliferation is followed by the migration of smooth muscle cells across the internal elastic lamina and formation of a neointima over the next few days. Initially, most of the neointimal cells are replicating. Intimal replication declines over a period of days and weeks, although the neointima remains hyperproliferative, at least in response to the infusion of angiotensin II.9 Therefore, unlike primary coronary artery lesions that have a near-occlusive neointimal mass, these rat experiments serve as a model for the initial formation of an intima. This process, the formation of a neointima, may or may not be relevant to the processes leading to restenosis in a vessel that already has an atherosclerotic intima. The failure of rat carotid artery models to
predict useful drug therapies to prevent restenosis in humans is consistent with the results of other experiments in larger animals. For example, although converting enzyme inhibitors work in the rat model, their failure to work in humans is consistent with a lack of efficacy in a swine model of arterial injury.\textsuperscript{10,11} Identifying the factors that create such disparities in animal models may yield clues to the mechanisms of arterial repair in humans.

The first step in reconciling the human response with that of animal models is to determine how closely the human time course of response to arterial injury, namely angioplasty, resembles what has been reported in animals.\textsuperscript{5,12} Therefore, the purpose of this study was to use directional coronary atherectomy–derived tissue to determine the proliferative profile, as reflected by immunocytochemical labeling for the proliferating cell nuclear antigen (PCNA), in primary and restenotic lesions.

Materials and Methods

Atherectomy Specimens

Primary and restenotic coronary artery specimens were obtained from 211 consecutive patients who underwent directional coronary atherectomy (Simpson Coronary Atherocath, Devices for Vascular Intervention, Inc, Redwood City, Calif) in the cardiac catheterization laboratories of the University of Washington Medical Center and Sequoia Hospital between September 1990 and August 1992. Multiple pieces of atherosomatous tissue weighing approximately 10 to 30 mg were obtained from each lesion. Several or all tissue pieces were immediately immersed in methyl Carnoy’s fixative for up to 14 days. Tissue was then paraffin-embedded, processed according to conventional techniques, cut into 5-\(\mu\)m-thick serial sections, and placed on glass slides.

Patient Clinical Profile

Patients with primary coronary artery lesions. Ninety-eight men and 20 women (median age, 62 years; range, 41 to 81 years) underwent directional coronary atherectomy of a total of 118 primary lesions. One hundred three lesions were in native coronary arteries (five from the left main coronary artery, 60 from the left anterior coronary artery, 14 from the left circumflex coronary artery, and 24 from the right coronary artery), with the remainder being in aortocoronary saphenous venous bypass grafts. Fifty-four patients presented with unstable angina pectoris; 64 patients had stable angina pectoris. Thirteen patients were receiving intravenous heparin therapy, and 9 patients were taking an angiotensin-converting enzyme inhibitor at the time of atherectomy.

Patients with restenotic coronary artery lesions. Seventy-five males and 18 females (median age, 61 years; range, 37 to 81 years) underwent directional coronary atherectomy of a total of 100 restenotic lesions (7 patients had two atherectomy procedures for either recurrent restenosis of the same lesion or restenosis of a different lesion). Ninety-four specimens were removed from native coronary arteries (3% from the left main coronary artery, 51% from the left anterior descending coronary artery, 12% from the left circumflex coronary artery, and 34% from the right coronary artery), with an additional six specimens being derived from aortocoronary saphenous venous bypass grafts. Fifty-six percent of patients had chronic angina pectoris, 44% had unstable angina, 13% were on intravenous heparin therapy, and 6% were taking an angiotensin-converting enzyme inhibitor at the time of atherectomy.

Immunocytochemistry

Single label anti-PCNA immunocytochemistry. One slide from each atherectomy tissue specimen block was labeled with an anti-PCNA antibody to screen for proliferating cells.\textsuperscript{13} Briefly, this involved deparaffinizing sections, blocking endogenous peroxidase activity with \(H_2O_2\), and applying the primary PCNA antibody (PC10 immunoglobulin [Ig] G, 1:1000 dilution, DAKO Corp, Carpinteria, Calif) for 60 minutes. A biotinylated anti-mouse secondary antibody was then applied for 30 minutes, followed by an avidin-biotin-peroxidase conjugate (ABC Elite, Vector Laboratories, Inc, Burlingame, Calif) for 30 minutes at room temperature. Standard peroxidase enzyme substrate, 3,3’-diaminobenzidine with nickel chloride was then added to yield a black reaction product. The slides were counterstained with methyl green. For each PCNA immunocytochemistry run, a slide with rat small intestinal basal epithelial crypts was used as a positive control. According to previous validation studies from this laboratory, antibody labeling was considered positive if the nuclei of the epithelial crypt cells were labeled dark black.\textsuperscript{13} Hence, only atherectomy specimen cells with the entire nuclei labeled dark black were considered PCNA-positive (Fig 1).

Double-label immunocytochemistry. If PCNA-positive cells could be identified on an atherectomy tissue slide by light microscopy at \(\times 400\) magnification, adjacent tissue sections from the same block were then prepared for double labeling with PCNA and a cell type–specific antibody. Briefly, the single-label procedure was performed as described above, with 3,3’-diaminobenzidine and nickel chloride being added to yield a black reaction product. After washing, sections were incubated with the second primary antibody or lectin overnight. Specifically, these reagents included the following: anti–smooth muscle \(\alpha\)-actin (1:500 dilution, Boehringer Mannheim Corp, Indianapolis, Ind) to identify smooth muscle cells, anti–CD-68 (DAKO-CD-68, KP1, 1:500 dilution, DAKO) to identify macrophages, and the lectin Ulex europaeus agglutinin I (1:500 dilution, Vector Laboratories) to identify endothelial cells. This was followed by sequentially incubating with biotinylated anti-mouse IgG or anti-Ulex IgG (Vector) and an avidin-biotin-alkaline phosphatase complex (Vector). The alkaline phosphatase was then developed with the standard ABC substrate kit (Vector) to yield a red reaction product and then counterstained with methyl green.

Cell Counting

The total number of PCNA-positive cells per slide was counted at \(\times 400\) light magnification with the investigator blinded to the clinical details pertaining to the specimens. The total numbers of nuclei present on 18 PCNA-positive and 19 PCNA-negative atherectomy slides were counted using a computerized image analysis system (BioScan Optimus, BioScan, Inc, Edmonds, Wash). Each double-labeled slide with tissue fragments
that included 10 or more PCNA-positive nuclei was counted manually to determine both the total number of PCNA-positive nuclei per fragment and the number of cells that labeled for PCNA and for a specific cell identity marker. The ratio of the total number of double-labeled cells to total number of PCNA-labeled nuclei was used to indicate the percentage of either macrophages, smooth muscle cells, or endothelial cells that were proliferating in each fragment.

**Statistical Methods**

All data are reported as mean±SD. The total numbers of cells on the primary and restenotic slides that were counted were compared by Student's *t* test. The frequencies of PCNA-positive cells in the primary and restenotic groups were compared by *χ²* test. To determine if the number of PCNA-positive cells in a specimen varied with the time interval after the initial coronary interventional procedure, the specimens were ranked according to four arbitrary time periods, and Spearman's rank correlation coefficient was computed.

**Results**

**PCNA Labeling**

The vast majority of atherectomy specimens from either primary or restenotic lesions showed no evidence of PCNA-labeled cells (Fig 2). Because the frequency of PCNA-positive cells and the number of slides showing any replicating cells at all were both very low, we restricted our counting to the number of positively labeled cells per slide. The total number of cells present on a typical slide was estimated by counting cell nuclei using image analysis. On 19 PCNA-positive and 18 PCNA-negative slides, the mean number of nuclei per slide was 4452±6110 and 4847±4458, respectively (*P*=0.83). Since the total number of cells on a typical PCNA-positive or -negative slide was similar, we conducted our subsequent analyses by counting only the number of cells per slide that labeled positively for PCNA.

Ninety-seven (82%) of 118 primary specimens and 74 (74%) of 100 restenotic specimens had no evidence of PCNA labeling on the entire slide (*P*=0.21). The remaining specimens from either group had varying numbers of PCNA-positive cells per slide, with the majority of slides having fewer than 50 positive cells. Although...
the frequency was low, 26% of the restenotic specimens had some PCNA labeling detected over a wide time interval after the initial procedure (eg, 1 to 390 days) (Fig 3). On the basis of the mean number of nuclei per slide, the vast majority of these specimens had ≤1% of all cells labeled PCNA-positive.

Because of possible relevance to the kinetics of the response seen in the rat, we focused particular attention on the proliferative profile of restenotic specimens collected within 2 months of a previous interventional coronary procedure. Only 12 of 30 specimens obtained within 60 days of the initial coronary interventional procedure had one or more PCNA-positive nuclei per slide. There was no difference in the proliferative profile of restenotic specimens collected in the first 3 months, 4 to 6 months, 7 to 9 months, or >9 months after the initial interventional procedure (Spearman’s rank correlation coefficient, 0.081; \( P=0.43 \)). Furthermore, PCNA labeling was found to be low, independent of whether the initial procedure was a percutaneous transluminal coronary angioplasty or a directional coronary atherectomy. We considered the possibility that the absence of a replicative index akin to the rat carotid artery model might be due to a redistribution of mass with angioplasty compared with a more extensive injury associated with the cutting action of atherectomy. However, on examining the PCNA index of nine specimens collected from patients within 6 days of the initial procedure (five atherectomies and four angioplasties), all postatherectomy specimens were devoid of PCNA labeling, and three of the postangioplasty specimens were PCNA-positive with 1, 7, and 20 PCNA-positive cells per slide each.

Identity of PCNA-Positive Nuclei

PCNA-positive smooth muscle cells, macrophages, and endothelial cells were identified in both primary and restenotic specimens (Fig 4). Since the typical atherectomy slide contains several tissue fragments, we focused our attention on the relative abundance and distribution of these cells in fragments with more than 10 PCNA-positive nuclei. Most PCNA-positive slides had at least one or two fragments with 10 or more PCNA-positive cells. However, because of the small size of many of the original atherectomy tissue blocks, it proved difficult to obtain three representative adjacent sections for double labeling for all PCNA-positive specimens. In some instances, tissue fragments were torn with sectioning; other specimens were so thin that serial sections did not provide tissue fragments that could be used for comparison purposes. From a total of 17 primary and 27 restenotic PCNA-positive specimens, 12 and 11 fragments, respectively, were used for double-labeling studies. In all PCNA-positive primary and restenotic fragments, PCNA-positive smooth muscle cells were detected. Similarly, PCNA-positive macrophages were detectable in 10 of 12 primary and all 11 restenotic fragments. Nine of 12 primary and 6 of 11 restenotic fragments had PCNA-labeled endothelial cells. Comparing the mean±SD percentage of each PCNA-positive cell type in the primary vs the restenotic fragments, respectively, the following results were obtained: smooth muscle cells, 62.7±21.3% vs 63.5±21.3% (\( P=0.93 \)); macrophages, 32.5±20.2% vs 24.9±18.8% (\( P=0.36 \)); and endothelial cells, 11.5±11.1% vs 14.6±15.3% (\( P=0.58 \)). PCNA-positive cells were found to be distributed in two distinct patterns: (1) collections of PCNA-positive endothelial cells surrounded by PCNA-positive macrophage and smooth muscle cells and (2) dispersed arrays of PCNA-positive smooth muscle cells devoid of other cell types.

Discussion

This study indicates that proliferation in primary and restenotic coronary atherectomy specimens, as indicated by immunocytochemical labeling for PCNA, occurs infrequently and at low levels. By use of antibody double labeling, these proliferating cells were identified not only as smooth muscle cells but also as macrophage and endothelial cells. The low frequency of replication and the absence of replication in the majority of specimens may explain why the rat carotid artery model has been an insufficient predictor of the efficacy of therapeutic interventions aimed at preventing restenosis.

Since humans cannot readily be labeled with tritiated thymidine or bromodeoxyuridine, our ability to assess cell replication depends on the use of a technique that identifies replicating cells by the characteristic presence of a cell cycle–specific antigen. PCNA is a highly conserved auxiliary protein of mammalian DNA polymerase-δ that is synthesized in the S phase of the cell cycle but may also be present in G1 and G2 phases.14,15 The regulation of PCNA expression is complex, with both transcriptional and posttranscriptional levels of involvement.16 Furthermore, the regulation of PCNA expression in quiescent cells differs from that in contin-
uously cycling cells. In contrast to the dramatic activation of PCNA synthesis in quiescent cells that are stimulated to proliferate, there is only a twofold to threefold variation in the synthesis of PCNA mRNA and protein in continuously cycling cells.

We considered the possibility that the relatively low PCNA labeling rate of these atherectomy specimens was due to false-negative labeling. Two recent smaller studies have used PCNA labeling to assess proliferation in atherectomy-derived restenotic specimens and found opposing results. In contrast to the results reported here, Pickering et al found that all restenotic coronary and peripheral arterial specimens had surprisingly high percentages of cells that were considered PCNA positive as measured by either immunocytochemistry (15.2±13.6%) or in situ hybridization (20.6±18.2%). However, only 4 of the 19 restenotic atherectomy specimens reported by Pickering et al were obtained from coronary artery lesions, and none were obtained within 1 month of the initial interventional procedure (eg, 1.6, 5.2, 6.1, and 7.9 months). (In unpublished studies, we have found PCNA labeling to be higher and more frequent in 20 peripheral atherectomy specimens compared with the 100 coronary atherectomy specimens reported in this study.) Moreover, the labeling indexes reported by Pickering et al seem exceptionally high (eg, as high as 59% of cells being PCNA positive) and resemble those of malignant neoplasms. Furthermore, unlike the present study, which used intestinal crypt epithelium, the study of Pickering et al lacked a positive control reference tissue with a known replication rate, thereby making the subjective interpretation of PCNA positivity difficult. Although it might be valuable to compare the Pickering protocol with an in vivo labeling study using tritiated thymidine, it seems at least likely that mean PCNA labeling indexes of 15% to 20% must greatly overestimate the replication rates in atherosclerotic coronary arteries, where small changes in vessel wall mass can result in dramatic changes in residual luminal diameter. Conversely, Strauss et al found no PCNA labeling in atherectomy specimens derived from one stented coronary artery and three stented saphenous venous bypass grafts that had succumbed to restenosis. This result is especially surprising, since stents provide a clear marker for identification of newly formed tissue.

The discrepancies among these different studies may reflect the need for control experiments with PCNA labeling. By immunocytochemistry, proliferating cells show increased PCNA labeling as compared with mitotically quiescent cells. Previous studies of injured arterial tissue using the protocol described in the present study have shown good correlation of PCNA immunolabeling with thymidine or bromodeoxyuridine incorporation. The inclusion of rat small intestine as a positive control tissue with each PCNA immunocytochemistry run provided evidence that the antibody was routinely labeling the nuclei of highly proliferating crypt epithelium PCNA-positive. Moreover, our PCNA index for primary atherosclerotic tissue is in close agreement with the tritiated thymidine labeling index determined by incubating atherosclerotic tissue in vitro. In addition, there is circumstantial evidence from one right coronary atherectomy specimen not reported in this study that our PCNA labeling methodology was appropriate. This specimen was not included in this study because it contained a mixture of tissue from a lesion that had been atherectomized 18 days previously, as well as a de novo more distal lesion that probably arose from arterial trauma with the initial more proximal atherectomy, and had 198 PCNA-positive cells out of a total of 10,049 cells (1.9%). This percentage is higher than for all other specimens reported in the study and may represent the consequences of arterial trauma to a relatively disease-free segment of artery—a response somewhat analogous to the more robust proliferation observed in the rat carotid artery balloon model. Finally, one criticism of PCNA labeling relative to other proliferative measurements is that it is likely to be oversensitive in detecting proliferative cells, since PCNA is expressed through a broader period of cell cycle traverse. Therefore, if anti-PCNA antibodies are overlabeling proliferating cells, the degree of proliferation in these atherectomy specimens may actually be lower than the already minimal levels that we have measured.

The low level of PCNA labeling seen in the primary coronary artery lesions is not surprising. Gordon et al examined coronary arteries obtained from patients with ischemic cardiomyopathies undergoing cardiac transplantation and found that typically less than 1% of the cells were labeled PCNA-positive. Furthermore, cell culture experiments have shown that human smooth muscle cells derived from atherosclerotic plaques grow slowly and appear to undergo a finite number of population doublings. More recently, angiographic studies have indicated that the progression of mild to moderate primary coronary artery lesions is a relatively slow process (eg, <20% degree stenosis per year). Even if the entire process of progression were due to smooth muscle replication, a growth rate this low would imply only one doubling per 5 years. Although restenosis is a much more rapid process, it is important to realize that very few doublings are needed to make a considerable mass. For example, one doubling a week of a 1-mm³ mass will produce a 1-cm³ mass in under 3 months. Thus, a fairly small portion of a lesion that doubles infrequently could contribute a large amount of mass to an artery that is already diseased. Such a time course, however, would be entirely different from that seen in the rat carotid artery injury model and would certainly be at odds with other reports of proliferation in restenotic coronary arteries. One reason to think that proliferation is present in these specimens is the histological appearance of restenotic tissue in areas characterized by stellate-shaped smooth muscle cells surrounded by a loose connective tissue matrix. Several observers have claimed that this pattern represents new tissue that has arisen from intimal hyperplasia. Unfortunately, areas with this morphology are not unique to restenosis and have been well described in the primary lesion. Although we did find areas fitting this description in our restenotic specimens, they were typically devoid of replication as assessed by PCNA labeling (Fig 5).

Apart from questions about the absolute levels of replication as measured by PCNA labeling, it is very important to point out that our data do not support the hypothesis that replication in restenotic tissue is any higher than the levels seen in the original plaque. PCNA
labeling was not detectable in 74% of restenotic atherectomy specimens and was not measurably different from that seen in atherectomy specimens from primary lesions. Moreover, there was no evidence of variation in the proliferative profile over the period following angioplasty. Those specimens that did display PCNA labeling were obtained over a broad restenotic time interval (e.g., 24 hours to over 1 year after the primary procedure) and typically had less than 50 PCNA-positive cells per slide. From counting 37 slides,

**Fig 4.** Double-label immunocytochemistry of coronary atherectomy specimens showing proliferating cell nuclear antigen (PCNA)-positive nuclei labeled dark black and the cytoplasm of cells identified with a cell-specific antibody in red. A methyl green nuclear counterstain was used to demonstrate the PCNA-negative nuclei. A. Anti-PCNA and anti-smooth muscle α-actin antibody labeling of proliferating smooth muscle cells (arrowheads) in a restenotic lesion of the right coronary artery approximately 1 year after the initial intervention. B. Anti-PCNA and anti-CD-68 antibody labeling of proliferating macrophage (arrowheads) in a primary lesion of the left anterior descending coronary artery. The top of the figure shows an area of dense connective tissue (DCT) suggestive of the fibrous cap, with a collection of macrophage (red cytoplasm) below. C. Anti-PCNA and anti-Ulex europaeus antibody labeling of proliferating endothelial cells (arrowheads) in a restenotic right coronary artery lesion obtained 90 days after the initial intervention.
the average total number of cells per slide was found to be approximately 4600. Therefore, the majority of slides had 1.0% or fewer cells that were PCNA-positive. For all PCNA-positive slides studied, there was no difference in the relative abundance of specific PCNA-positive cell types in primary compared with restenotic specimens.

Our failure to find a time course of replication similar to that seen in the rat requires that we consider possible sources of error in our human studies. Tissue sample selection bias is a major concern. The depth of vessel wall that is cut and the amount of tissue recovered have an obvious influence on the conclusions that can be drawn about the lesion. Typically, the interventional

Fig 5. Proliferating cell nuclear antigen (PCNA) labeling of hypercellular restenotic coronary atherectomy tissue, with a homogenous collection of stellate smooth muscle cells surrounded by an abundant extracellular matrix. A, Hematoxylin and eosin stain (original magnification ×100). B, Higher power of same tissue fragment (original magnification ×400). C, Adjacent slide showing same tissue fragment labeled with anti-PCNA antibody and a methyl green counterstain (original magnification ×100). Note the lack of proliferation based on the absence of PCNA-labeled dark nuclei.
cardiologist cuts the lesion in all four quadrants of the vessel circumference (even for some eccentric lesions). According to the practices of the cardiologists who contributed atherecomy specimens to this study, as much plaque as possible was removed until the lesion looked suitably "debulk." In fact, it is likely that atherecomy removes preexisting atherosclerotic plaque, any "new" restenotic mass (if it exists), and the lesion margins. Therefore, given the potential heterogeneity of the specimens, we have included an extensive number to look for trends and to reduce any background or spurious results. Alternatively, one might argue that cellular proliferation does occur after the initial procedure but only in the relatively less accessible media or adventitia. Although this is possible, it is important to note that coronary atherecomy removes portions of adventitia in as many as 30% of procedures and therefore should pick up deeper proliferative pockets in the vessel wall. Finally, our data do not rule out a potential role for proliferation in the early time interval after the initial procedure. Of nine specimens collected within 6 days of the initial procedure, only three had evidence of PCNA labeling with 1, 7, and 20 PCNA-positive cells, respectively. (Although not reported in this study because of differences in fixation, we have also examined five formalin-fixed specimens collected within 13 days of the initial procedure and found two with evidence of PCNA labeling.) Therefore, we may simply lack enough specimens in this period to demonstrate a brief proliferative spike.

If the kinetics of neointimal formation in the rat are a poor model for the sequence of events seen in humans, what then are the key events that lead to postprocedural luminal narrowing? First, these data do not rule out a major role for replication, although it may occur at a low level. Typically, restenosis occurs 3 to 6 months after the primary procedure—a time interval long enough for indolent cell replication to produce a considerable cell mass. Even if primary and restenotic lesions have similar replication rates, differences in rates of cell death could accelerate growth of the restenotic tissue. Second, it is possible that the restenotic tissue specimens represent an acceleration of the normal atherosclerotic process. This may involve more of an alteration in gene expression than a predominately proliferative response and may be particularly relevant to those plaque regions characterized by near-homogenous collections of stellate-shaped smooth muscle cells surrounded by abundant extracellular matrix. The sequence of events that results in the production of this space occupying matrix might be key to understanding lesion progression. Finally, it may be useful to liken an atherecomy to wound debridement. The wound response, including the forces generating wound contraction, occurs at the edges of the wound and may play an important role in the stenosis of the vessel wall.

In summary, PCNA labeling of primary and restenotic human coronary atherecomy specimens indicates that proliferation occurs infrequently and at low levels. These findings may help explain why antiproliferative therapies have not been effective in retarding the progression of primary lesions or preventing restenosis from occurring. Future study of the events that result in lesion progression will require careful evaluation of the role of various molecules in lesions, not only for mitogenetic potential but also for control of smooth muscle cell migration and matrix production, angiogenesis, thrombosis, and vasoconstriction. Animal models will require the production of primary lesions that resemble those of humans before meaningful therapeutic experiments can be conducted in the field of restenosis research.

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