Editorial Comment

Chemical Atherectomy
A Novel Approach to Restenosis

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Since its introduction in 1977, percutaneous transluminal coronary angioplasty (PTCA) has become an increasingly used treatment of coronary artery disease. In 1983, 39,000 procedures were performed; nearly 150,000 were performed in 1987, and it is estimated that the number could exceed 500,000 per year in the next few years. With this rapid increase in usage, angiographic success rates have steadily improved. According to the statistics kept by the National Heart, Lung, and Blood Institute’s PTCA Registry, success rates in the years from 1977 to 1986 were 67% and increased to 88% in the years from 1980 to 1986. This is despite the fact that the patients in the latter group were older and had increased incidence of multivessel disease, poorer left ventricular function, and increased incidence of prior myocardial infarction.

Even with the increased numbers and success, restenosis at the site of angioplasty has remained a persistent problem. Numerous attempts to reduce its incidence have not met with success. In their report of the first 133 patients with successful angioplasty, Gruentzig et al reported a restenosis rate of 30% within the first 6 months. This number has not varied in more recent studies, with restenosis rates between 25% and 35% reported in numerous studies.

Two mechanisms have been reported to contribute to restenosis: early platelet aggregation and thrombus formation and late neointimal smooth muscle proliferation. The former process appears to be caused by platelet aggregation on the denuded intimal surface after balloon injury, whereas considerable evidence supports the concept that migration and proliferation of medial smooth muscle cells into the intima is the major cause of late restenosis. Careful angiographic studies have demonstrated that the peak incidence of restenosis occurs between 2 and 3 months after angioplasty, and numerous autopsy studies from that period have demonstrated that the restenotic lesion consists almost entirely of smooth muscle cells. Although the relation between the two processes is not clear, numerous lines of evidence do not support a major role for platelets in the development of the restenosis that occurs 2 to 3 months after the procedure. Autopsy studies have failed to demonstrate thrombus in the restenotic lesions, platelet deposition, although seen immediately after injury, is not seen at later times, and a prospective trial of aspirin and dipyridamole failed to alter the restenosis rates although they did markedly reduce the incidence of myocardial infarction with PTCA.

From the above discussion it is clear that to affect restenosis, one important component must be the ability to control smooth muscle cell growth. To do this, an understanding of the response of the smooth muscle cell after balloon injury is needed. After balloon injury, there is a migration of medial smooth muscle cells into the intima and an increase in the labeling of cells with 3H-thymidine, indicating dividing cells. This increase in labeling is seen in approximately 50% of the cells and peaks between 3 and 14 days after injury. The cause of this increase in growth is unclear and appears to be extremely complex, involving numerous growth factors.

After injury, smooth muscle cells undergo a phenotypic change, which, for simplicity, can be thought of as a change from a contractile to a synthetic phenotype. This change is accompanied by an increase in the expression of numerous genes. A number of these genes are associated with the platelet-derived growth factor (PDGF) family. Smooth muscle cells cultured from the intima after balloon injury secrete increased amounts of a PDGF-like activity when compared with cells derived from the media, and an increase in PDGF β-receptor and PDGF A-chain messenger RNA (mRNA) expression is seen in the vessel wall in the same model. One factor that could contribute to this increase in PDGF A-chain expression and secretion is the vasoconstrictor peptide angiotensin II. We have demonstrated that angiotensinogen mRNA, the precursor for angiotensin II, is locally expressed in the vessel wall, and when angiotensin II is added to smooth muscle cells in culture, there is an increase in PDGF A-chain mRNA levels as well as an increase of PDGF-like...
material released into the media. Based on these findings, Powell et al demonstrated that treatment of rats with a converting enzyme inhibitor attenuated neointimal proliferation after carotid artery balloon injury. These findings suggest that an autocrine pathway in which angiotensin II–induced increases in PDGF result in further smooth muscle cell growth is important in the intact animal.

It is clear that PDGF is not the entire story. Substantial evidence also indicates that basic fibroblast growth factor (bFGF) is involved in this process. Expression of both bFGF and bFGF receptors has been reported after vascular injury, and this growth factor has been shown to stimulate endothelial regrowth and proliferation in denuded arteries. There is also evidence that insulinlike growth factor I (IGF-I) is involved, as it is a potent smooth muscle mitogen and its mRNA is induced after balloon catheter injury of the rat aorta. Other factors such as interleukin-1, interleukin-6, IFN-2, and transforming growth factor-β have also been implicated in the smooth muscle response to injury.

It is simplistic to assume that all of these growth factors and cytokines act alone. There is ample evidence in the literature that they can interact with each other and in some cases are synergistic. It is not surprising, therefore, that trials of nonspecific growth inhibitors such as corticosteroids or specific PDGF antagonists such as trapidil have not been overly successful. For these reasons, the report in this issue of Circulation by Epstein et al offers a unique and exciting possibility for the treatment of restenosis. The authors have taken advantage of the fact that when the smooth muscle cells migrate from the media to the intima and begin to grow, they undergo a phenotypic change accompanied by the expression of new genes. One of these genes, as demonstrated in this article and elsewhere, is the gene for the epidermal growth factor (EGF) receptor. This increase is not subtle; nongrowing, quiescent cells in culture express about 4,200 receptors per cell, whereas rapidly proliferating cells express about 44,000 receptors per cell.

The authors have used this fact, coupled with the knowledge that cancerous cells expressing an increased number of receptors could be selectively targeted, to create a molecule that will be toxic only to rapidly proliferating smooth muscle cells. By removing the cell recognition domain of the gene for Pseudomonas exotoxin A, they have created a new protein that is toxic to cells only in very high doses because it can no longer be internalized into cells. Internalization is essential for its action because the exotoxin inhibits protein synthesis by interfering with the addition of amino acids to growing protein chains. To this truncated gene they have linked the complementary DNA for transforming growth factor (TGF) α, creating the chimeric gene TGFα-PE40. Because TGFα is recognized by the EGF receptor, this new protein can now be internalized only into cells expressing the EGF receptor and, therefore, will kill only rapidly proliferating smooth muscle cells. This is dramatically illustrated by the ID50 values, which are 125 ng/ml for quiescent cells but only 4.0 ng/ml for growing cells. This selectivity for growing cells was not seen with the native intact exotoxin. Specificity was demonstrated by the ability of EGF, which competitively blocks internalization of the TGFα-PE40 protein by binding to its receptor, to abolish the killing effect of TGFα-PE40 and also by the lack of any effect by a mutated TGFα-PE40.

Although these studies are quite exciting, a number of questions remain unanswered. The present study was performed in cultured cells, and the act of culturing causes smooth muscle cells to change their phenotype. It remains to be demonstrated whether the differences in EGF receptor expression seen in the cultured cells, which is essential for this technique, will also be seen in smooth muscle cells after balloon injury in vivo. Even if the EGF receptor is newly expressed after balloon injury, selectivity in vivo must still be demonstrated so that toxicity to other proliferating tissue can be avoided.

It should also be mentioned that a similar technique has been reported in abstract form by Cassells et al, who used a conjugation of bFGF coupled to the plant toxin saporin to selectively kill rapidly proliferating smooth muscle cells expressing the bFGF receptor. Despite some problems, these two studies represent what appears to be novel and potentially extremely useful methods to inhibit smooth muscle cell growth. The concept of killing growing cells using a nonspecific toxin made highly specific by its conjugation to a specific protein circumvents the complexity of the restenosis process, which certainly involves numerous growth factors and cytokines. With an estimated 500,000 PTCA’s performed per year and an estimated restenosis rate of 30%, a successful treatment could benefit 150,000 patients per year in the United States alone. Although TGFα-PE40 may not turn out to be effective in vivo, it is the concept that is exciting and certainly holds great promise for the future.

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References

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