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Pharmacological Approaches to the Prevention of Restenosis Following Angioplasty
The Search for the Holy Grail? (Part II)†

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Contents

Summary Part I of this article reviewed the results of studies investigating the effectiveness of antithrombotic, antiplatelet, antiproliferative, anti-inflammatory, calcium channel blocker and lipid-lowering drugs in preventing or reducing restenosis after angioplasty.

However, despite 15 years of clinical experience and research in the field of restenosis prevention, this has not yet resulted in the revelation of unequivocal beneficial effects of any particular drug. Other newer approaches likely to receive more attention in the future include antibodies to growth factors, gene transfer therapy and antisense oligonucleotides. Whether there is a feasible monotherapy, whether we have to focus on a drug combination, or whether we are only searching for 'the Holy Grail' remain to be answered.

4. Future Directions

Molecular biology has provided us with detailed information about an important family of 'peptide cell regulator factors' (PRF) [Green 1989; Majesky et al. 1990; Michell 1989; Ross 1989; Schneider & Parker 1990; Waterfield 1989]. Although it seems to be a long way from the bedside of the patient, this new family could lead to drugs that prevent restenosis after percutaneous transluminal coronary angioplasty (PTCA). In recent years it has become clear that cell proliferation and differentiation are controlled by many peptides and other agents through their interactions with cell surface receptors that send signals to the cell interior.

† Part I of this article appeared in the previous issue of the Journal.

4.1 Antibodies to Growth Factors and Inositol Diphosphate

Platelet-derived growth factor (PDGF) has been shown to stimulate smooth muscle cell migration in an *in vivo* system. Intravenous infusion of PDGF for one week resulted in a 15-fold increase in intimal lesion area following injury with a filament loop catheter. In addition, analysis of autoradiograms after supplementation of [^{3}H]thymidine demonstrated a 4-fold increase in dividing cells and a 20-fold increase in nondividing cells, suggesting the increase in cell number is due mainly to migration (Jawien et al. 1991).

Ferns et al. (1991) used goat polyclonal antibodies to PDGF to examine the formation of intimal lesions in de-endothelialised dilated rat carotid arteries, and administered anti-PDGF before and 9 days after the procedure. This resulted in a 40.9% reduction in the area of the neointima ($p < 0.01$). A [^{3}H]thymidine test showed no significant difference in labelling indices, and so suggests that the decrease in initial area is primarily due to reduction of chemotactic migration. The lack of effect on mitogenesis is probably the effect of endogenously produced PDGF-AA, a homodimer peptide chain that in *in vitro* studies needs larger amounts of anti-PDGF than PDGF-AB or -BB to block mitogenic activity (Raines et al. 1989).

Transforming growth factor-β (TGF-β) can either stimulate or retard cell growth, depending on concentration, cell age and density. Majesky et al. (1991) showed in a rat carotid artery model increased TGF-β synthesis after balloon injury, which stimulated smooth muscle cell proliferation. Of particular interest is the report by Nikol et al. (1992) who observed the *in vitro* expression of TGF-β in primary atherosclerotic and restenotic lesions. TGF-β may be involved in an exaggerated repair response following vessel wall injury.

Shah et al. (1992) injected antibodies to TGF-β in disrupted dermal tissue in rats and investigated the wound healing process. Scar tissue of the treated animals had a lower rate of angiogenesis and infiltration of macrophages, which can release their TGF-β stores. Furthermore, the collagen and fibronectin fibres of this tissue were found to have a smaller volume and normal orientation. Bonan et al. (1992b) described the *in situ* delivery anti–TGF-β antibodies in the coronary arteries of 5 minipigs. The extent of vessel wall injury, however, as well as the restenosis injury index (ratio of neointimal area to the total wall area over extent of injury) was the same in treated and untreated animals. This study suggests an ineffective role for TGF-β antagonism.

Epstein et al. (1991) linked the nonspecific but effective *Pseudomonas* exotoxin A, lacking its cell recognition site (PE40), to TGF-α. This growth factor is recognised by the EGF receptor, present in abundance on rapidly proliferating smooth muscle cells. Due to this new recognition site, PE40 is able to attach to cells expressing this EGF receptor, be internalised, and inhibit protein synthesis. The PE40-TGF-α complex has an extreme affinity to cells expressing the EGF receptor. In the same way, Casscells et al. (1990) used a saporin-FGF conjugate to inhibit DNA synthesis and intimal thickening in injured vessels.

Basic FGF is another mitogen, synthesised in both endothelial and smooth muscle cells, and is thought to be stored in the subendothelial matrix (Vlodavsky et al. 1987). Administration of an antibody to FGF reduced smooth muscle cell proliferation in animals (Lindner & Reidy 1991).

All of the above results suggest a significant role of growth factors in the response of smooth muscle cells to vessel wall injury.

Among the important signals that have been implicated in these processes are the phosphorylation of tyrosine residues on proteins (fig. 4) and changes in the intracellular concentrations of the messenger molecules cAMP, diacylglycerol, inositol-1,4,5-triphosphate (IP3) and Ca^{++}, which directly or indirectly exert most of their regulation on the phosphorylation and dephosphorylation of serine and threonine residues of particular proteins (Michell 1989). Recent studies have demonstrated that mitogens such as PDGF and thrombin rapidly induce the hydrolysis of phospatidylinositol biphosphate (PIP2) by phospholipase C (Michell 1989; Takenawa & Fukami 1989).

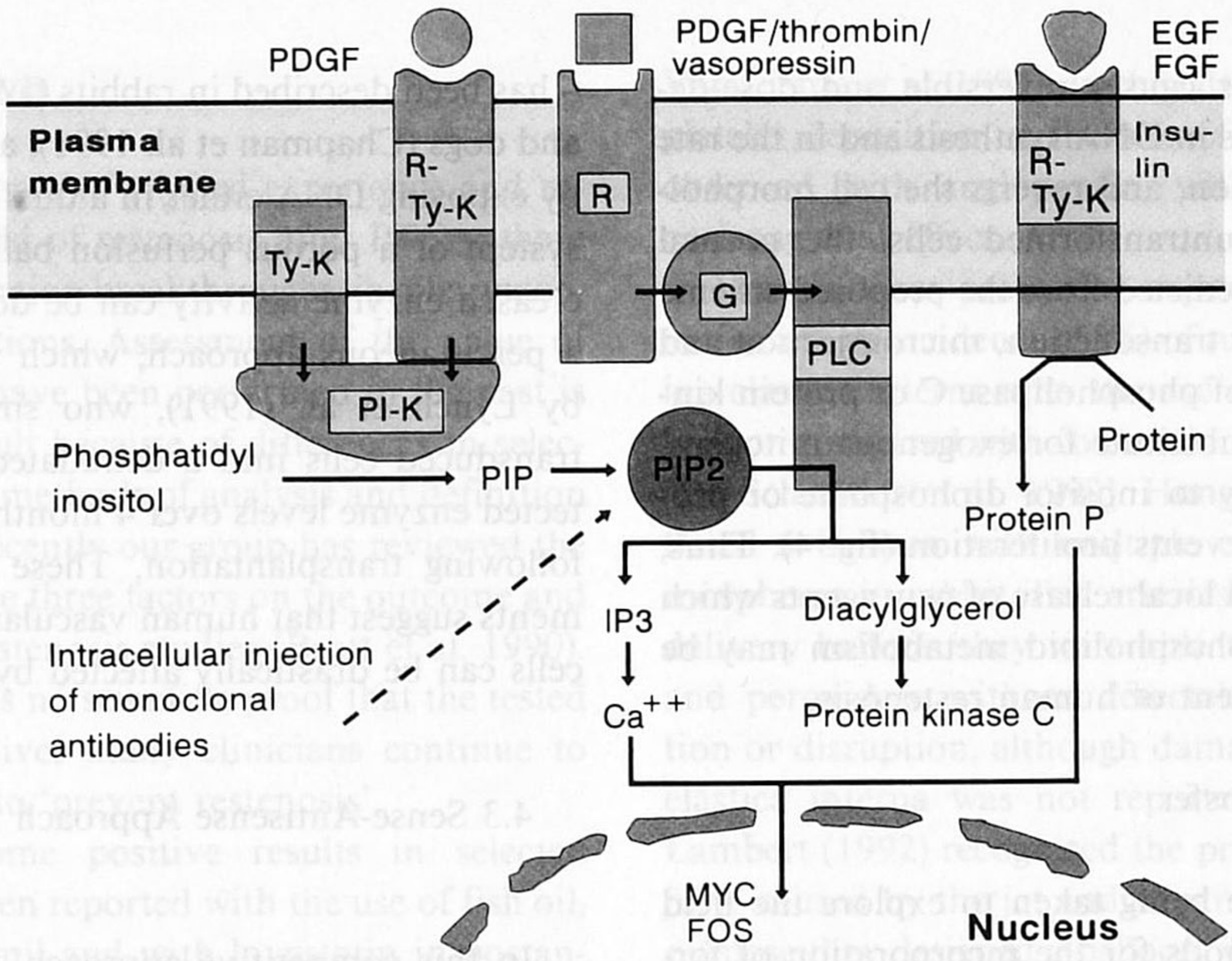

Fig. 4. Schematic representation of the phosphorylation and hydrolysis of phosphatidyl inositol (PI) and the conversion to inositol triphosphate (IP3) and diacyl glycerol. Several mitogens rapidly induce this process by stimulating phospholipase C (PLC). Regulation of cytosolic calcium ion (Ca^{++}) concentration is central to cell growth control. Stimuli to the nucleus result in MYC and FOS expression, oncogenes that initiate proliferation and phenotype changes. The dotted arrow indicates the target of the monoclonal antibodies against phosphatidyl inositol biphosphate (PIP2), which Takenawa et al. (1989) used to prevent cell proliferation. *Abbreviations:* Ty = tyrosine; K = kinase; R = receptor; G = guanine; EGF = epidermal growth factor; FGF = fibroblastic growth factor; PDGF = platelet-derived growth factor.

PIP2 hydrolysis produces two compounds. The first of these is IP3, a water-soluble molecule whose formation triggers the mobilisation of Ca^{++} in the cytoplasm. Within cells there is a membrane compartment, probably a part of or closely related to the endoplasmic reticulum, into which Ca^{++} is continuously pumped by an ATP-driven pump, so maintaining the cytoplasmic concentration at approximately 0.1 μmol/L. When receptors trigger the formation of IP3, it binds to IP3 receptors on the membrane enclosing this reservoir, thus opening channels through which Ca^{++} is released to raise the cytoplasmic Ca^{++} concentration to somewhere in the range of 0.2 to 0.1 μmol/L within seconds. It has long been known that regulation of cytosolic Ca^{++} levels is central to control of cell growth, and that this regulation may go awry in malignantly transformed cells. The second product of PIP2 hydrolysis is 1,2-diacylglycerol; this compound activates one or more of the protein kinase C (fig. 4).

These signalling pathways have been considered to play important roles in cellular responses. Unfortunately, they are not the sole signal transduction system. At least four structural classes of growth factor receptors have been identified, all of which phosphorylate on tyrosine residues. It is not clear to what extent these different tyrosine kinases share the same protein substrate. In some cases the ligand binding and tyrosine kinase domains of a receptor protein are separate portions of a single polypeptide chain that spares the plasma membrane, whereas in others these sites are on separate subunits of a multisubunit membrane-spanning receptor protein. In this system there is clear evidence that receptors transmit their information to the phospholipase C via a coupling protein G (guanine-nucleotide–dependent) [fig. 4].

A Japanese group (Takenawa & Fukami 1989) has developed a monoclonal antibody against PIP2. Microintracellular injection of the antibody into

transformed cells causes reversible and dose-dependent decreases in DNA synthesis and in the rate of cell proliferation, and reverts the cell morphology to that of untransformed cells, the normal phenotype. As predicted from the proposed scheme for growth factor transduction, microinjection and overproduction of phospholipase C or protein kinase C also can substitute for exogenous mitogens, whereas antibody to inositol diphosphate or protein kinase C prevents proliferation (fig. 4). Thus, development and local release of new agents which inhibit inositol-phospholipid metabolism may be useful for treatment of human restenosis.

4.2 Gene Transfer

First steps are being taken to explore the field of genetics. Methods for the incorporation of foreign DNA into endothelial and vascular smooth muscle cells have been developed recently and could be useful in protecting vessels from vascular diseases, including atherosclerosis and restenosis. The most elegant way to deal with this sophisticated technique is to augment genetic sequences, leaving the defective host genes unaltered.

Transfection can be achieved by physical means such as microinjection (Anderson et al. 1980) or electroporation (Neumann et al. 1982), or by a chemical approach, using liposomes as carriers (Felgner et al. 1987). A commonly used medium is the replication-defective retroviral vector, although amphotropic adeno- and DNA-viruses can be used also. The advantage of defective retroviruses is that these produce efficient infection followed by integration, and hence stable gene expression. In 1989, Nabel and colleagues succeeded in *in vitro* implantation of genetically modified endothelial cells expressing β-galactosidase using a double balloon system to introduce the cells. Histochemical staining of this enzyme was observed in the intimal layer several weeks later and thus proved gene expression.

Introduction of new genetic material into the wall of coronary arteries can give rise to the detection of enzyme activity. Transfection of luciferase – an enzyme not expressed in mammalian cells – has been described in rabbits (Leclerc et al. 1991) and dogs (Chapman et al. 1991), and was achieved by exposing DNA either in a dual balloon catheter system or a porous perfusion balloon system. Increased enzyme activity can be detected following a percutaneous approach, which was also proved by Lynch et al. (1991), who simply introduced transduced cells into a denudated artery and detected enzyme levels over 4 months of observation following transplantation. These recent developments suggest that human vascular smooth muscle cells can be drastically affected by gene therapy.

4.3 Sense-Antisense Approach

In this competitive approach, oligonucleotides are used to block messenger RNA action. This antisense technology has been used to inhibit c-myc protein production in haematopoietic cells (Holt et al. 1988), resulting in an inhibition of proliferation. Simons and Rosenberg (1992) demonstrated that smooth muscle cell proliferation, results in an elevation of c-myb messenger RNA levels, and the generation of the oncogene c-myb. This oncogene is critically important in the change of the phenotype and in cell growth regulation. Interfering in the process of intimal hyperplasia at the postnuclear level might give us the possibility to block one specific cell response.

Simons et al. (1992) used rat carotid arteries to investigate the role of c-myb and oncogene suppression by its complementary antisense oligonucleotide in neointimal formation *in vivo*. The sense oligonucleotide or the corresponding antisense molecule was applied locally to the injured vessel wall in a plurionic gel, and resulted in minimal intimal smooth muscle cell accumulation, in contrast to the controls.

Alteration of proto-oncogene expression is a very attractive concept, and the developments in this field might result in a complete interruption of the hyperplastic response of intimal tissue, at the level of the ultimate common pathway.

5. Conclusions

Despite 13 years of clinical experience and research in the field of restenosis after PTCA, there have been no major breakthroughs in pharmacological interventions. Assessment of the value of drug trials that have been performed in the past is extremely difficult because of differences in selection of patients, methods of analysis and definition of restenosis. Recently our group has reviewed the influence of these three factors on the outcome and conclusion of restenosis studies (Beatt et al. 1990). Although there is no scientific proof that the tested drugs are effective, many clinicians continue to prescribe them to 'prevent restenosis'.

However, some positive results in selected patients have been reported with the use of fish oil, trapidil, verapamil and with lovastatin in postangioplasty patients. Furthermore, we seem to have found an animal model that more closely mimics the restenotic lesion found in humans (Schwartz et al. 1991b). In the near future the results will be known of ongoing multicentre trials investigating ACE inhibition, serotonin antagonists, hirudin, low molecular weight heparins, angiopeptin and other promising drugs such as inhibitors of thrombin production, growth factor blockers, prostacyclin analogues and monoclonal antibodies against platelet membrane receptors (GP IIb/IIIa) and von Willebrand factor. The outcome of these trials may bring us closer to the solution of the restenosis problem.

Investigators are also looking for local drug delivery systems that allow adequate local drug concentrations without adverse systemic side effects. Wolinsky and Thurg (1990) demonstrated the feasibility of delivering potentially therapeutic agents, ranging from small molecular weight dyes to proteoglycans like heparin into the vascular wall. For this purpose they used a perforated catheter and an injection/inflation pressure up to 5 bar, and demonstrated that pharmacological agents can be selectively delivered to the arterial media and intima. Several other experimental studies have been recently carried out using the microporous balloon technique (Hong et al. 1991; Kaplan et al. 1991a; Van Lierde et al. 1991). In the latter study, reduced platelet deposition at the site of angioplasty was observed with angiopeptin, without a systemic anticoagulant effect.

Despite these promising experiments, there remains a high incidence (55%) of rupture of the lamina elastica interna after the use of a microporous balloon compared with conventional balloons (29%) [De Scheerder et al. 1992]. Hong et al. (1992) inflated a balloon with multiple channels to 6 atmospheres in rabbit iliac arteries. Using this drug delivery balloon they were able to deliver insulin and peroxidase without detectable media dissection or disruption, although damage to the lamina elastica interna was not reported. The group of Lambert (1992) recognised the problem of wall injury, caused by the jet and stream effects. For this purpose they designed a balloon with minimal pore size and maximal pore density. Balloon inflations during 30 seconds to 5 atmospheres in several artery models were performed. Analysis by light microscopy and scanning electron microscopy, revealed endothelial denudation, without clear subendothelial trauma. Proper deposition of the dye was tested by videodensitometric measurements, as well as by microscopic cross sectional analysis.

De Scheerder et al. (1992) furthermore reported the rapid loss of drug from the vessel wall, possibly due to the lack of specific receptors. Only during the first 20 minutes after the start of drug delivery were the measured tissue concentrations greater than plasma concentrations.

A perfusion balloon with 32 pores on the surface which allowed pressure-mediated drug delivery has been evaluated using a dye in place of a drug (Ruiz et al. 1992). No mechanical damage to the vessel wall was seen at the site of balloon inflation, while the test dye penetrated to the media and in one animal to the adventitia.

Wilensky et al. (1991b) employed microparticles as carriers for drugs. This microcarrier drug delivery system could prohibit rapid elimination by the increased network of vasa vasorum in atherosclerotic lesions that causes early outward diffusion. For this study they injected polystyrene particles, 5μm in diameter, which appeared to be

deposited in the intimal and medial layers and the adventitia, and which could still be detected after an interval of 14 days. Recently, this delivery system containing dexamethasone was successfully applied in rat carotid arteries (Villa et al. 1993) [see section 3.4.1].

Red blood cells have also been investigated as a microcarrier system (Yellayi et al. 1991). Heparin was bound effectively to red blood cells *in vitro* during heating. This concept to deliver drugs to the arterial wall has to be explored further.

Cox et al. (1991) used balloon expandable stents, coated with heparin and/or methotrexate in coronary arteries of animals. Although they could not show significant differences in smooth muscle cell proliferation, they demonstrated local release of drug over a 3-week period. The idea of bioabsorbable stents is receiving attention in *in vitro* studies. Bier et al. (1991) studied a stent, constructed of purified type I collagen, which expands by hydration assisted by balloon inflation. Lumen diameter was moderately reduced without any substantial blood flow reduction. Ebecke et al. (1991) used the biodegradable polymer poly-*l*-lactide. Release of pharmacological agents was dependent of the molecular weight of the poly-*l*-lactide used.

These developments, combining temporary vessel dilatation and slow local release of pharmacological agents, seem to possess promising potential in the research against restenosis.

At this moment, enormous efforts are being put into the search for a treatment modality that will solve the problem of restenosis. Experimental and clinical research continues to attempt to find a drug that prevents restenosis in the long term. The more we discover regarding the underlying mechanisms, the more opportunities there are for further research. Whether this endeavour is only searching for 'the Holy Grail', or whether there is a feasible drug treatment that works on the process of restenosis, without serious adverse effects, remains uncertain.

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