Therapeutic approaches to the control of fibrocellular intimal hyperplasia after angioplasty

Enthusiasm for the technique of percutaneous transluminal coronary angioplasty has been tempered by the realization that 25–50% of patients have a recurrence of their symptoms in 3–6 months because of restenosis at the site of the original atheromatous lesion.1 This is due not to local thrombosis or to the reaccumulation of atheroma but to a rapid growth of vascular smooth muscle cells, both within the intima and migrating from the media, which produces a new lesion known as fibrocellular intimal hyperplasia (FCIH).2 There is probably some degree of FCIH in all patients after angioplasty; and its rate of development and final quantity determine the recurrence of angina. FCIH is not unique to the vessel injured by a balloon catheter: intimal hyperplasia is a feature of the “onion skin” lesion of malignant hypertension and systemic sclerosis, the plexiform lesion in the pulmonary arterioles in pulmonary hypertension, and late vein graft occlusion.3 More recently intimal hyperplasia has been identified as the cause of the diffuse vascular disease which occurs after cardiac transplantation4 and it is the main cause of graft failure after 5 years. The vessel wall seems to have a single response to various insults on the endothelium, media, and adventitia. These insults include chronic immunological injury, sustained pressure increases, rheological changes, or direct physical distension.

Animal models
There has been considerable debate about the relevance of established animal models of FCIH to the clinical problems, particularly to restenosis after angioplasty.5 In some species—for example, the rat—the normal intima consists of only a layer of endothelium and so the vascular smooth muscle cells in FCIH must be derived from the media, while in others, such as humans and the pig, the intima is much more substantial and does contain vascular smooth muscle cells. The contribution of the intimal vascular smooth muscle cells and of cells such as macrophages within the atheromatous plaque to the subsequent development of FCIH is not known. Atheroma has a complex pathology and is many years in the making. The best models of its genesis are expensive and have given us only limited insight.6 FCIH on the other hand seems to develop relatively rapidly, particularly after angioplasty when it is established within weeks or a few months. Animal models of FCIH can be easily induced by vascular distension with a Fogarty balloon catheter or angioplasty catheter. The histological appearance of FCIH varies somewhat between species but the accumulation of vascular smooth muscle cells, and extracellular matrix is characteristic of the lesion.7 Smooth muscle cells within the lesion have a different phenotype from that of quiescent medial vascular smooth muscle cells, there being a change in the contractile protein isoforms, increased cellular synthetic apparatus, and increased motility of cultured cells derived from the lesion.6–8 Synthesis of matrix proteins, such as tenasin, is increased9 and tissue type plasminogen activator and urokinase are expressed by the smooth muscle cells of the injured vessel.10 Endothelial regrowth may be incomplete though the luminal smooth muscle cells become flattened and superficially are similar in appearance to the endothelium.7,11 There is evidence also of persistent impairment of endothelial cell function.12

Clinical trials
The development of restenosis at the lesion site in patients undergoing angioplasty has been markedly resistant to empirical drug treatment: corticosteroids, aspirin, fish oils, calcium channel blockers, and angiotensin converting enzyme inhibitors have all been tried without success.13 The results of studies of the effects of hirudin or self-administered subcutaneous heparin are awaited and a further trial is planned to investigate the therapeutic potential of monoclonal antibodies to the platelet adhesion molecule GIIb/IIIa.

Pathogenesis
Examination of the nature of the injury produced by the balloon dilatation gives some insight into the pathogenesis of the restenotic lesion. The atheroma is compressed into the wall of the artery but the process, by necessity, also destroys or damages the overlying endothelium and stretches the media and adventitia. Some degree of dissection is probably inevitable.2 There is evidence from both experimental models of angioplasty14 and from clinical audit15 that the development of FCIH is related to the amount of distension of the vessel by the balloon. In the clinical situation this is difficult to control precisely because of the relief of the patient’s symptoms requires that the lumen size is increased and displacement of the atheroma adds to the direct pressure from the balloon catheter.

Much of the research into the pathogenesis of FCIH after balloon catheter injury has focused on the role of various autocrine and paracrine growth factors and cytokines. As might be expected with an injury that causes stripping of the endothelium and direct physical damage to medial vascular smooth muscle cells and adventitial nerves and vasa vasora, the mediator involvement is complex. Platelet derived growth factor (PDGF),16 basic fibroblast growth factor (bFGF),17 transforming growth factor beta (TGF-β)18 and interleukin-1-alpha19 are among the many factors that have been implicated in the
pathogenesis of FCIH. Clearly the response to the balloon catheter injury of the vessel is so fundamental that complex interacting cascades of growth factors ensure the development of FCIH and it is unlikely that a single pivotal factor amenable to pharmacological intervention will be easily identified. In the rat model of FCIH high doses of angiotensin converting enzyme inhibitors substantially inhibit intimal thickening after balloon catheter injury of the rat carotid artery but clinically relevant doses of ACE inhibitors did not affect the incidence of restenosis after coronary angioplasty. It may be that the stimulatory cascades of growth factors and cytokines in humans and in the rat have a different balance that influences the response of the lesion to drugs.

New approaches to prevention

Nevertheless, FCIH develops because of proliferation and migration of vascular smooth muscle cells. However, this response is likely to involve mechanisms fundamental to growth and repair and control of FCIH will probably necessitate the local application of agents that will inhibit either or both proliferation and migration. These may be pharmacological, physical (for example radiation) or genetic. Transfection of cells for subsequent transfection and direct transfection into the arterial wall of marker genes such as β-galactosidase, luciferase, and human adenosine deaminase and genes of proteins with therapeutic potential such as tissue plasminogen activator has already been demonstrated. Simons et al successfully inhibited FCIH induced by Fogarty balloon catheter dilatation of the rat carotid by the application of a phosphothiolated antisense c-myc oligonucleotide to the adventitial surface of the injured vessel (figure). The proto-oncogenes such as c-fos, c-myc and c-myc are universally expressed during cell division and may be induced by a wide range of stimuli including physical stresses. Antisense oligonucleotides are short lengths of single stranded DNA that are complementary (antisense) to lengths of DNA in part of the target gene or to the RNA transcript from it. The oligonucleotides inhibit the function of the gene by binding to these sequences. Chemical modification of the oligonucleotides confers resistance to degradation by nucleases and improves stability. Targeting the early cellular responses to injury may minimise any possible inter-species differences in the pathogenesis of the lesion but genes expressed uniquely by proliferating or migrating vascular smooth muscle cells may be more specific targets.

Simons et al delivered their synthetic antisense oligonucleotides to the adventitial surface of the injured vessel and clearly this would not be feasible for routine clinical use. However, administration of the therapeutic agents directly to the vessel wall requires only minor modification of catheter hardware already available. Such modifications include double balloons to isolate the segment of artery into which the therapeutic agent is infused via a central pore, microperforation of the balloon to allow instillation of agents into the wall, and perfusion systems to permit distal blood flow during the procedure (though instillation of the transfection vector or the oligonucleotide may take only a few minutes). The duration of activity of the modified antisense oligonucleotides or of the duration of expression of transfected genes of proposed therapeutic function, and the longer term effects of retroviral transfection vectors will have to be ascertained before such agents can be applied to humans. Animal models of FCIH will have a pivotal role in these studies and costing, handling, and housing advantages make the rat the natural choice for primary studies though confirmatory studies in pigs or primates may follow. It can be envisaged that in the future percutaneous transluminal coronary angioplasty will be coupled to the local application of a therapeutic agent aimed at inhibiting the development of FCIH and resulting restenosis.

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