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Induction of vascular atrophy as a novel approach to treating restenosis. A review

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Abstract

Regardless of the type of arterial reconstruction, luminal narrowing (stenosis or restenosis) develops in approximately one third of the vessels. In the past, the focus of research has been on the mechanisms of stenosis (intimal hyperplasia, pathologic remodeling) and pharmacologic approaches to prevention. An alternative approach is to induce intimal atrophy after luminal narrowing has developed, thus limiting treatment to only those patients that develop a problem. This approach to treat established disease by reducing wall mass through induction of cell death and extracellular matrix removal would be particularly useful for treating stenosis in synthetic bypass grafts or stented vessels, in which intimal hyperplasia is the primary mechanism of stenosis. This approach may be applicable as well to other vascular proliferative disorders, such as pulmonary hypertension and chronic transplant arteriopathy. Proof of principle has been shown in experiments with antibodies to PDGF receptors that cause neointimal regression in baboon PTFE grafts and with ACE inhibitors that induce medial atrophy in hypertensive arteries. Possible molecular targets could include PDGF receptors, A20, and BMP4. Further studies are needed to determine the utility of such a therapeutic approach to vascular disease.

INTRODUCTION

Arterial occlusive diseases are treated by various open and endovascular approaches including bypass graft, endarterectomy, atherectomy, balloon angioplasty and stent angioplasty. Regardless of the type of intervention, stenosis or restenosis develops in a significant number of patients, often leading to limb loss or death[1,2].

Research on restenosis has focused on the biological mechanisms of vascular hyperplasia caused by vascular injury and on pharmacological strategies to prevent hyperplasia. Drug eluting stents are a successful application of these strategies, although late stent thrombosis may be a result of inhibiting endothelial cell healing as well as smooth muscle cell (SMC) proliferation[3]. An alternative approach might be to induce intimal atrophy after restenosis has developed. This approach would be particularly useful for treating stenotic and restenotic disease in synthetic bypass grafts or stented vessels, since restenosis in these rigid vessels only

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involves intimal hyperplasia and not vessel remodeling. Furthermore, it would permit the surgeons to treat only the subset of patients with restenosis. Since patients with restenosis often have symptoms (worsening claudication or angina), they are easily identified. This strategy might also be applied to pulmonary arterial hypertension and chronic transplant arteriopathy, which share the pathophysiologic features of increased arterial wall mass and luminal narrowing. In this review, we will summarize the evidence that vascular hyperplasia is reversible and that a strategy to reduce wall mass through inhibition of proliferation and induction of cell death and extracellular matrix loss could be applied to many vascular disorders. As background we will first briefly review mechanisms of vascular hyperplasia and hypertrophy.

Mechanisms of Vascular Hyperplasia and Hypertrophy

The vascular response to injury has been studied in animal models for four decades and the cellular and molecular mechanisms of intimal hyperplasia and medial hypertrophy are understood in some detail[4,5]. For example, mechanical or hemodynamic endothelial injury (e.g. after angioplasty and stent or vein graft placement) may expose the subendothelial matrix and induce platelet adhesion, aggregation and activation. Activated platelets release various cytokines, chemokines and growth factors, which initiate SMC proliferation, leukocyte recruitment and activation of the coagulation cascade. Substances released or activated after injury include platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β interleukin (IL)-1, IL-6, IL-8, thrombin, adenosine diphosphate, and thromboxane A2. The maximal intimal response requires medial damage, as well as endothelial cell injury[6]. Indeed, SMCs around the area of injury begin to undergo apoptosis within 1 hour of injury, and while blockade of apoptosis after endothelial and medial injury inhibits intimal hyperplasia[7], SMC apoptosis without endothelial injury does not lead to intimal hyperplasia[8].

Rat medial SMCs begin to proliferate within 48 hours[9]. Fibroblast growth factor (FGF)-2 plays a major role in this initial proliferative event. It is released from damaged endothelial and SMCs, and, while antibody blockade prevents the proliferation of SMC in the rat carotid media by ~80%[10], it has no effect on subsequent cell proliferation in the intima[11]. In contrast to the injured rat carotid in which PDGF plays a minor role in medial SMC proliferation[12], a blocking antibody to the PDGF receptor β inhibits medial SMC proliferation >90% in the baboon saphenous artery[13]. Other factors such as insulin-like growth factor (IGF)-1[14,15], thrombin[16], TGF- β[17] together with cytokines IL-1β[18] and IL-6 all contribute to SMC proliferation. A host of inhibitory factors also moderate the proliferative response to injury, such as adiponectin[19], heparan sulfate proteoglycans (e.g. perlecan[20]; syndecan-1[21]), interleukin 10[22], adrenomedullin[23] and somatostatin[24]. In addition, high blood flow inhibits intimal hyperplasia after arterial injury[25,26].

After 4 days, medial SMC proliferation reaches a peak in both rodent and primate models of injury and SMCs begin to migrate to the intima. PDGF clearly plays a major stimulatory role for SMC migration in both rodents[27] and primates.[28] It is released from platelets, and is also upregulated in the vessel wall[29] in endothelial cells, SMCs, and macrophages. Insulin[30], tissue factor[31] and FGF2[32] also contribute to SMC migration in vivo.

Intimal SMCs are derived primarily from the media, but they may also be derived from adventitial myofibroblasts, pericytes associated with infiltrating microvessels, and circulating progenitor cells[33,34]. Intimal SMCs proliferate for up to 2 weeks and begin to express major extracellular matrix (ECM) genes, such as elastin and collagen I, by approximately 7 days after injury [35]. The intima grows as elastin, collagen, glycoproteins and proteoglycans are synthesized and secreted. Between 1 and 3 months, a steady state is reached at which time the intima is ~20% cells and ~80% ECM[35].

The response of previously injured vessels to reinjury has also been investigated. Koyama and Reidy[36,37] observed intimal and medial SMC proliferation in response to a second balloon injury to the rat carotid, but found that the intimal thickening was entirely from increased ECM synthesis not SMCs. Hanke et al[38] performed balloon injury to the rabbit carotid previously injured by electrical stimulation. They found that proliferation continued at low but significant rates up to three weeks and that the number of intimal SMCs nearly doubled.

Vascular atrophy in normal development

Vessel regression is an essential aspect of the development of the vascular system, which includes the processes of vasculogenesis (de novo formation of blood vessels) and angiogenesis (budding of new vessels from preexisting vessels)[39,40]. Regression occurs during development after formation of a primary plexus of capillary-like vessels. In addition, after birth there is regression of the infrarenal aorta where blood flow decreases dramatically, leading to apoptosis and reduction of vessel diameter[41,42]. In addition, there is a postnatal loss of a network of vessels in the vitreous and around the lens of the eye. This latter vessel loss depends on macrophage-induced endothelial cell death[43]. These processes are orchestrated by physical forces, such as blood flow, as well as various stimulators and inhibitors whose expression is tightly regulated both in a temporal and spatial manner[44] and which are reinitiated in vascular disease in adults[45].

Regression is an inherent component of any angiogenic program[40]. For new vessels to bud off, stable quiescent vessels must first be destabilized. This process involves the loss of surrounding pericytes. At this stage the vessel can either form a new vessel or regress, a process controlled by relative activities of PI3 kinase and PLCγ[46]. The presence or absence of growth factors (e.g. VEGF) and other angiomodulators (e.g. endostatin), which can be controlled by proteinases like cathepsins[47], dictate the fate of the destabilized vessel.

While induction of microvessel regression may be a therapeutic strategy in many disorders associated with abnormal or excessive angiogenesis, such as cancer, psoriasis, arthritis, retinopathy, obesity and atherosclerosis[48], this anti-angiogenic strategy may not be applicable to larger vessels. Nevertheless, it may be possible to induce atrophy in large diseased arteries by various means described in the next section of this review.

Animal models of vascular atrophy

1. High blood flow-induced intimal atrophy

In normal arteries, an increase in blood flow causes acute vasodilation, a process that is dependent on endothelial release of nitric oxide (NO). Chronic adaptation to increased flow is also dependent on the endothelium[41]. However, because a rigid vessel, such as an artificial graft or calcified artery, cannot dilate, the only way to normalize shear stress is to reduce wall mass. We have investigated this possible mechanism of adaptation to increased blood flow. We have used a polytetraflouroethylene (PTFE) graft model in baboons, in which bilateral PTFE (internodal distance 60um, internal diameter 4mm) aorto-iliac bypass grafts are allowed to heal for 2 months. Unlike the reinforced 30um internodal distance PTFE grafts used clinically, these grafts uniformly heal by the transmural ingrowth of microvessels through the interstices of the PTFE. Complete endothelialization is achieved by 2 weeks, and maximal, evenly distributed neointimal thickening along the graft is complete by 2 months[49]. When blood flow and shear stress are increased by the creation of a distal femoral arteriovenous fistula, the neointima regresses markedly in the graft, but there is no regression in the normal, adjacent iliac artery[50,51]. It appears that vessels attempt to maintain shear stress at a constant level between 5 and 25 dynes/cm^2 by altering luminal area. The downstream iliac artery, which does not undergo atrophy, increases both overall and lumenal area in response to increased

flow without any change in wall mass. The sequence of events leading to neointimal loss is shown in figure 1.

Neointimal SMC death increases and SMC proliferation declines by 1 day after fistula placement[52]. There is also evidence of ECM degradation beginning at 4 days associated with a proportional loss of cells. There is a particular loss of the ECM proteoglycan versican[53, 54]. This is significant because the sulfate groups of the chondroitin sulfate (CS) glycosaminoglycan chains of of the βGAG domain of versican bind water. Thus early collapse of the neointima could be caused by glycosaminoglycan degradation and loss of water.

The mechanism of flow-mediated regression is not known. An interesting aspect of this baboon model is that, while there is a continuous endothelial layer, it is dividing at a much higher rate than in normal vessels. In baboons as well as humans, SMCs do not accumulate in grafts unless there is an endothelial layer and restenotic lesions usually are endothelialized. The requirement for endothelium in intimal regression has not been tested. However, while increased blood flow clearly inhibits neointimal hyperplasia in the absence of endothelium in rat arterial injury and graft models[2625] and there are unknown endothelium-independent vasodilators (not NO, cyclooxygenase products, cGMP, cAMP, or hypoxia-sensitive) mediating arterial dilation[55], regression of established lesions has only been reported for models with endothelium present. For example, Zhuang et al studied a rabbit model utilizing sequential phases of low flow intimal hyperplasia and high flow intimal regression in endothelialized carotid arteries[56]. In the baboon PTFE graft model, it is an important observation that SMCs only proliferate in the area adjacent to the endothelium[51], suggesting endothelial cell regulation of SMC function. Although endothelial cell eNOS is increased[50], inhibition of NOS function after the switch to high flow does not inhibit neointimal regression[51]. Other factors such as hemeoxygenase-1, which catalyses the formation of CO, is induced by high flow after one day (see online data[52]), and it may inhibit SMC proliferation via CO production[57].

2. Tight external wrap-induced medial atrophy

We have previously reported that rabbit vein grafts adapt to arterial pressure by increasing total cross-sectional area of the wall, SMC number, and ECM; this adaptation is suppressed when the grafts are wrapped tightly with PTFE.[58]. A rigid perivascular polyethylene cuff around the rabbit aorta causes medial, but not intimal, atrophy[59]. Medial atrophy is also observed in the carotid artery when another carotid artery is used as a cuff, thus proving the foreign body reaction is not required for medial atrophy[60]. We have recently reproduced these results in baboons; medial, and not intimal, atrophy in the baboon iliac artery can be induced in response to a PTFE wrap. This wrap is designed to limit expansion but not reduce luminal diameter. At 4 days, the tight wrap causes a proportional loss of cells and ECM, while by 28 days there is relatively more loss of ECM[61](unpublished data). In both rabbit and baboon the external cuff reduces circumferential strain. Decreased luminal diameter may also contribute to the atrophy process by increasing shear stress.

3. Neointimal and medial regression in an arterialized vein graft

Davies *et al* reported that wall thickening in vein bypass grafts placed in the arterial circulation of rabbits for 14 days regresses when the grafts are reimplanted into the venous circulation. Both intimal and medial areas decrease and are associated with apoptosis of SMC and a relative increase in collagen. These effects are caused by either a reduction in blood pressure or flow or both[62,63].

Regression of in-stent restenosis

Intimal atrophy occurs spontaneously in stented arteries after about 6 months in humans[64, 65] and pigs[66] and after about 2 months in rats[67]. At these late times in all three species[66–68], the neointimal ECM shows a relative loss of versican and a relative gain of collagen compared to earlier times. In addition, the data suggest that collagen is more tightly packed or changes from type III to type I. While human stent neointimas show a loss of SMCs at times greater than 18 months[68], these late times have not been studied in animals.

Recently Hong *et al* conducted an intravascular ultrasound study in humans and at 24 months observed both regression and progression of lesions first observed at 6 months after bare metal stent implantation[69]. While regression of the intima was observed in 76% of the lesions, progression was demonstrated in 24%. There is no clue as to why lesions regress or progress. However, these results changed the clinical treatment strategy of treatment of asymptomatic in-stent restenosis from deliberate intervention to careful observation and reintervention only in selected cases.

While it is clear that the neointima created by stent-mediated injury undergoes spontaneous regression, there is a lack of agreement on whether the intima of a traumatized artery in the absence of a stent undergoes intimal regression at late times[70,71]. One rat carotid injury study observed regression and one study did not. In the study in which late regression was observed[71] there was also a significant decrease in lumenal area before regression began. This constrictive remodeling might increase shear stress that may in turn mediate regression. This idea is supported by the observations of Zhuang et al[56], who studied the effects of multiple rounds of increasing and decreasing blood flow through the normal, uninjured rabbit carotid artery by opening and closing downstream arterio-venous fistulas. They observed that increased blood flow could cause neointimal regression in this arterial model as was observed in the baboon PTFE model.

Regression of cardiovascular hypertrophy in hypertension

Cardiovascular hypertrophy and hyperplasia are common features of hypertension and are important components of target organ damage. The regression of cardiovascular hypertrophy is now considered an important therapeutic objective to reduce the complications of hypertension[72,73]. In addition to lowering blood pressure, some antihypertensive drugs, such as losartan, enalapril and nifedipine, stimulate SMC apoptosis and reduce DNA synthesis, vascular mass and medial cell number in the thoracic aorta of spontaneously hypertensive rats (SHR), but not in normotensive Wistar Kyoto rats (WKY)[74]. This regression of medial hypertrophy in response to medication is also observed in hypertensive humans[75]. In balloon-injured arteries, nifedipine induces SMC apoptosis in established neointimas in both SHR and WKY rats and causes lesion regression[76]. DeBlois and Hamet have suggested that induction of SMC apoptosis might be an important way to reverse the structural changes in the vasculature caused by hypertension[77].

Primary pulmonary hypertension is a disorder characterized by hypertensive vasculopathy, vasoconstriction, and vascular wall remodeling. The histologic findings in idiopathic pulmonary hypertension are obliteration of the lumen of small- and medium-sized pulmonary arteries in association with medial hypertrophy, concentric laminar intimal fibrosis, fibrinoid degeneration, and formation of plexiform lesions and in situ thrombosis[78]. While the pathogenesis and genetic basis of this disease are poorly understood, it is now clear that mutations in a bone morphogenetic protein receptor predispose to both idiopathic and familial forms of the disease (see review by Said[79]). Current treatment relies on various pulmonary vasodilators.

The balance of cell proliferation and apoptosis in pulmonary artery SMC maintains the thickness and tissue mass of the arterial walls at an optimal level. If this balance is disturbed such that there is more proliferation or less apoptosis, the arterial wall thickens, narrowing the lumen and ultimately leading to the obliteration of the vessel and to an overall increased pulmonary vascular resistance. Prevention or reversal of constrictive vascular remodeling by inhibiting proliferation and promoting apoptosis in pulmonary artery SMC would be an effective future therapeutic modality.

In the monocrotaline rat model of pulmonary hypertension, inhibition of either elastase, matrix metalloproteinases, or the tyrosine kinase activity of the EGF receptor reduces expression of the SMC survival factor tenascin C, increases SMC apoptosis, and causes regression of the hypertrophied vessel wall by a coordinated loss of cells and ECM[80–82].

The structural changes associated with pulmonary hypertension can be reversed through reducing hemodynamic stress[83]. Of particular interest from the clinical perspective are the results of blockade of the tyrosine kinase activity of the PDGF receptors by Gleevec (imatinib mesylate). In both chronic hypoxia and monocrotaline models in rats and mice, Gleevec reverses the symptoms of pulmonary hypertension[84]. Based on this work, two case reports showed that Gleevec successfully reverses symptoms of idiopathic pulmonary hypertension in patients refractory to conventional treatments[85,86] leading to the suggestion by Patterson et al that selective PDGFR blockade may represent a novel therapy to target vascular remodeling in pulmonary arterial hypertension. Because Gleevec also blocks KIT, LCK, and ABL kinases to the same extent and others to a lessor degree[87], further work is required to determine the mechanism of action of this drug.

Regression of intimal hyperplasia in transplant arteriopathy

Transplant vasculopathy is characterized by concentric, heterogeneous proliferative thickening of the intima of the allograft vasculature and is initiated and propagated by both immunological and nonimmunological factors[88,89]. The main pathobiologic manifestations of the disease are the acquisition of an inflammatory endothelial phenotype, increased SMC proliferation, and defective SMC apoptosis. Bach et al reported that a number of cytoprotective genes, including antiapoptotic Bcl family members, Bcl-2 and Bcl-x_L, the heat shock protein heme oxygenase-1, and the zinc finger protein A20, are expressed in endothelium and SMCs of long-term surviving cardiac xenografts devoid of transplant arteriosclerosis[90]. These investigators proposed a cytoprotective recipe that provides the endothelium with potent anti-inflammatory, anticoagulant, and antiapoptotic potential and maintains the contractile medial SMC phenotype[91]. While there are reports in animal models showing that PDGFR blockade by Gleevec prevents the development of allograft arteriosclerosis in transplanted hearts[92–94], the definitive role of PDGF in the development of transplant vasculopathy is still unknown.

It may be possible to induce regression of transplant vasculopathy. One pharmacologic agent that has shown promise is sirolimus, a natural fermentation product produced by Streptomyces hygroscopicus. The cellular action of sirolimus (rapamycin) is mediated by binding to the FK506 binding protein-12 (FKBP-12)[95,96]. The resulting sirolimus/FKBP-12 complex inhibits the kinase activity of mammalian target of rapamycin (mTOR), subsequently increasing levels of the cyclin-dependent kinase inhibitor $p27^{Kip196-98}$ and reducing the activity of multiple kinases associated with mitogen-induced cell proliferation (e.g. $p70^{s6k}$, cyclin E/CDK-2). This leads to cell cycle arrest at the G1/S transition point[96,99–101]. Ruygrok et al reported a case of angiographic regression of aggressive cardiac allograft vasculopathy after 1 year of sirolimus treatment started 2 years post-transplantation[102]. Park et al reported regression of transplant coronary artery disease during chronic low-density lipoprotein-

apheresis[103]. They found a 7.9% increase of mean luminal diameter due to either atherosclerotic regression or vessel remodeling.

Strategies to induce vascular atrophy

The main pathologic features of vessel wall atrophy are loss of SMCs and ECM resulting from decreased SMC growth and matrix synthesis, SMC apoptosis, and ECM lysis. There are several molecular pathways that might be utilized to induce vascular atrophy.

1. Platelet-derived growth factors and receptors (PDGF/ PDGFR)

As discussed above, PDGF is a major regulator of SMC proliferation, migration, and ECM protein synthesis. Tanizawa et al [104] reported PDGF B chain and PDGFR β receptor were present by immunostaining and Ueda et al[105] found PDGF A and B chain were present by in situ after PCTA in coronaries. Blockade of PDGFR-β by antibodies inhibits intimal hyperplasia in injured arteries and PTFE grafts in baboons[28,106]. Although by itself it does not block the induction of intimal thickening, PDGFR-α blockade does cause a decrease in SMC density and number[106]. This latter effect is consistent with the known survival role of PDGF[107]. Of greater interest, however, is the observation that concomitant antibody blockade of PDGFR-α and -β induces atrophy of established intima in baboon PTFE grafts under normal flow conditions (figure 2)[108]. Simultaneous inhibition of cell proliferation and stimulation of cell death by the administration of antibodies to both PDGFR α and β is required to induce atrophy. While a fully humanized version of the chimeric antibody to PDGFR-β had no effect on restenosis in patients undergoing coronary stenting[109], it may be that simultaneous blockade of both receptors is required for an effect. This goal may be achieved with Gleevec, a PDGFR kinase inhibitor that appears to reverse pulmonary vascular hypertrophy and pulmonary hypertension and might have a similar effect on intima in vascular reconstructions.

2. Bone morphogenic protein 4 (BMP4) and its inhibitor noggin

BMPs are members of the transforming growth factor (TGF)-β superfamily that regulate cell proliferation, migration, differentiation, and apoptosis. High shear stress induces BMP4 mRNA and protein expression in the PTFE graft neointima in baboons, while noggin (a BMP inhibitor) is decreased. BMP4 inhibits SMC proliferation *in vitro*, an effect blocked by noggin. Thus the increase in BMP4 coupled with a decrease noggin may contribute to graft neointimal atrophy by inhibiting SMC proliferation and increasing SMC death[52].

3. A20

A20 is a zinc finger protein induced by tumor necrosis factor-α, interleukin-1 or CD-40 cross-linking in a variety of cell types[110]. A20 prevents intimal hyperplasia when transfected acutely, but induces regression when transfected in established intimal lesions of the injured rat carotid artery[111]. Expression of A20 in medial SMC prevents neointima formation by shutting down inflammatory and proliferative responses of SMC via inhibition of NF-κB and increased expression of the cell cycle dependent kinase inhibitors $p21^{waf1}$ and $p27^{kip1}$. SMCs are also sensitized by A20 to undergo apoptosis in response to cytokines and Fas/FasL via a NO-dependent mechanism. This causes regression of established neointimal lesions. In endothelial cells, A20 is anti-inflammatory by inhibiting NFκB like in SMCs, but unlike SMC it is antiapoptotic via inhibition of the proteolytic activation of caspase 8[112]. Therefore, A20 has protective effects for endothelial cells and proapoptotic effects for SMCs making it a good candidate for inducing vascular atrophy while minimizing endothelial damage[91].

4. Others

Recently we performed microarray analysis of our two vascular atrophy models in baboons, namely the PTFE graft, high flow-induced intimal atrophy model and the PTFE wrap-induced medial atrophy model. Of ~28,000 genes we found several genes commonly up- or down-regulated in both models. Upregulated genes included extracellular matrix degrading factors and possible growth regulatory factors. Downregulated genes included survival factors and matrix genes[113]. These molecules may have important roles in vascular atrophy and may lead to pharmacological treatments for established lesions.

Conclusion

After vascular reconstruction, luminal narrowing is in part caused by intimal thickening, the consequence of endothelial injury and inflammation, smooth muscle cell hyperplasia, and extracellular matrix accumulation. It may be possible to induce these lesions to shrink (figure 3). This novel approach to the treatment of restenosis is supported by animal experiments and a few clinical observations demonstrating vascular atrophy in response to drugs such as Gleevec. A potential limitation to this approach might be the formation of aneurysms. For example, it is known that venous or arterial aneurysms often form at arterio-venous fistulas and drug-eluting stents may cause aneurysms[114]. It is clear that a means for targeted delivery of limited duration would need to be developed. Additional studies are needed to determine whether this therapy will be broadly applicable.

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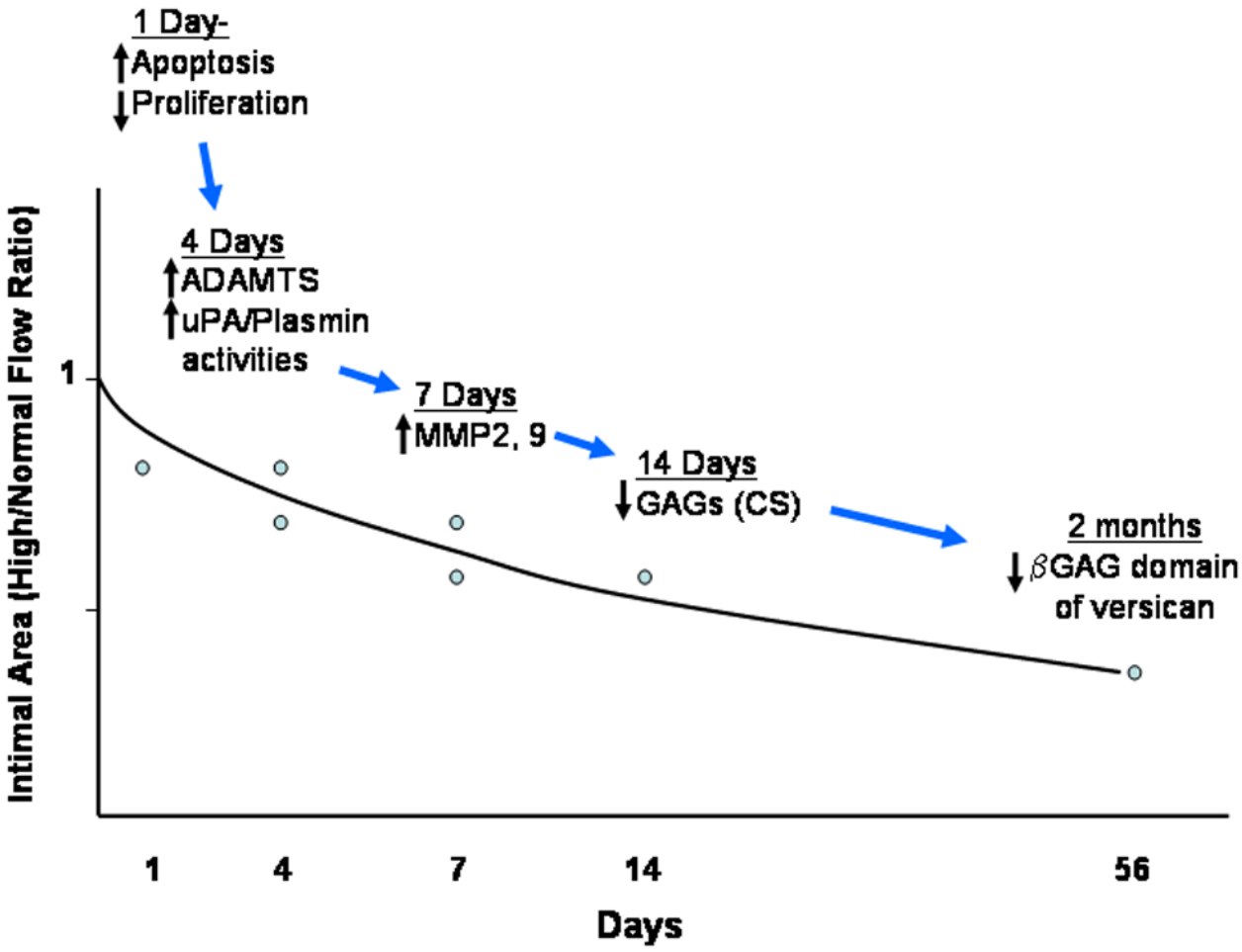
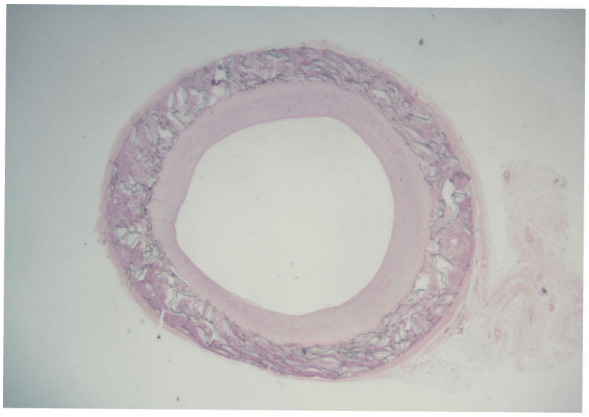


Figure 1.
Diagram of temporal changes in the neointima of the baboon PTFE aorto-iliac graft after the switch to high blood flow.



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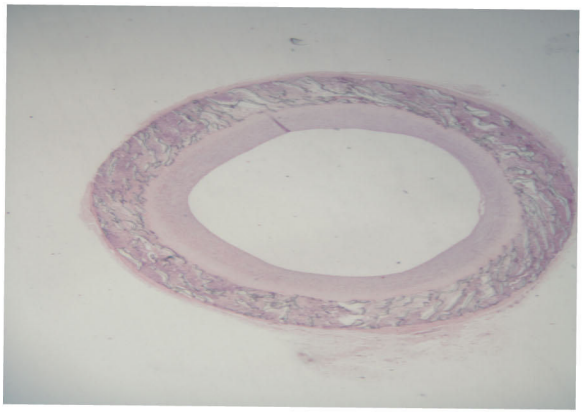

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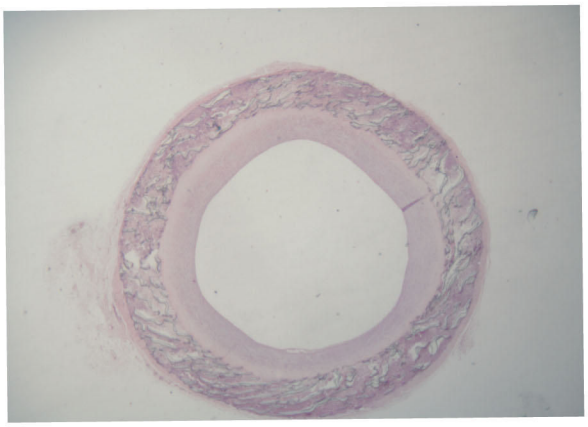

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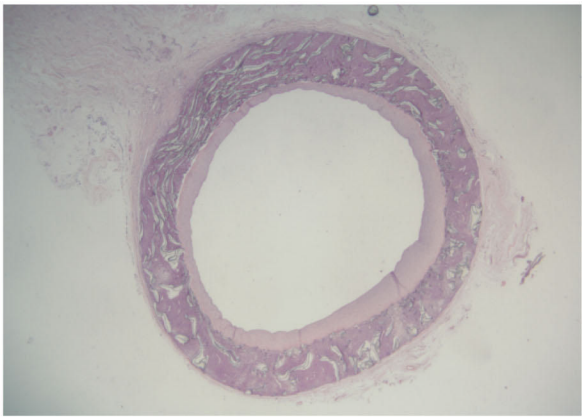

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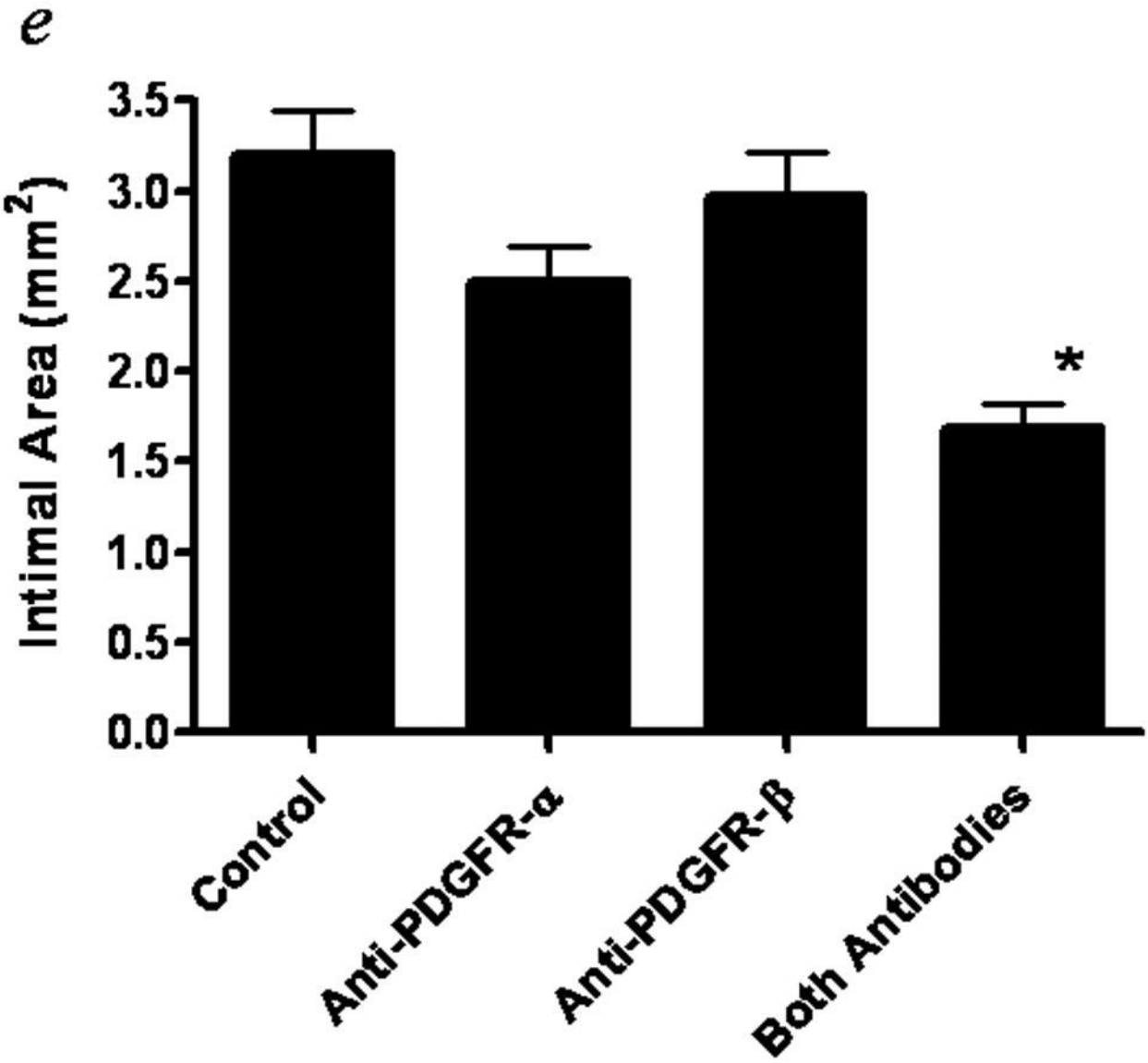

Figure 2.

Histologic cross sections of normal flow PTFE grafts at 2 weeks after initiation of treatment with vehicle control (a), blocking antibodies to PDGFR α (b), blocking antibodies to PDGFR β (c), or blocking antibodies to both PDGFR α and β (d). (hemotoxylin-eosin, 16X). Intimal areas of 4–7 animals per group are presented as the mean ± standard error (e). Reproduced from Engelsbe et al[93] by permission from Elsevier Publishing.

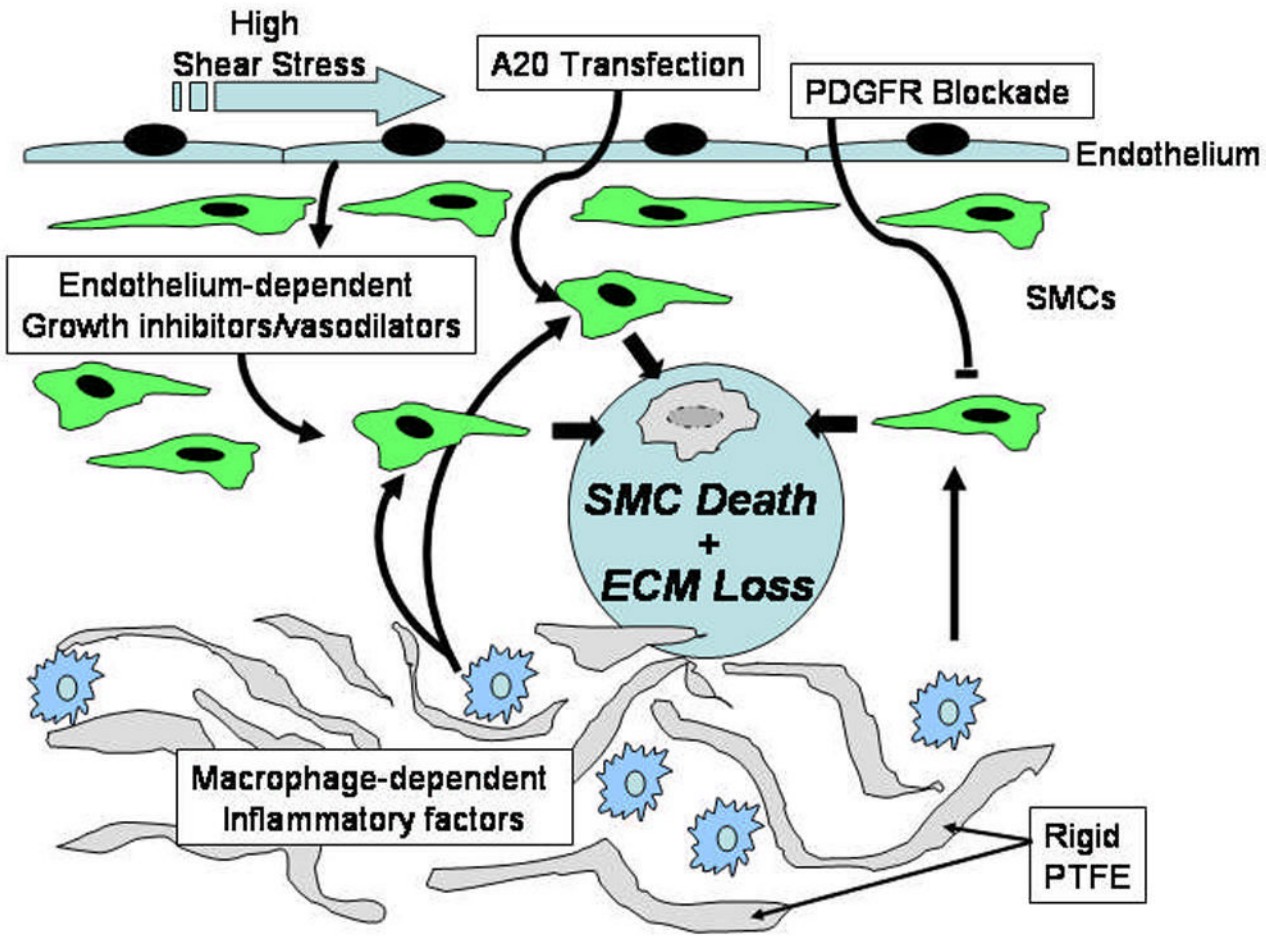

Figure 3.
Diagram of possible pathways of vascular regression. Either high shear stress, transfection of A20, or blockade of PDGFR in combination with inflammatory factors could cause regression of neointima.