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Review

Biological Mechanisms Influencing Prosthetic Bypass Graft Patency: Possible Targets for Modern Graft Design

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ABSTRACT

In recent years, ample attention has been directed towards the mechanisms that play a major role in the process of vascular graft failure, especially graft thrombosis and intimal narrowing have been highlighted. In this article, a survey is conducted into the key mechanisms of the biological processes of intimal hyperplasia and ultimate graft failure. The sequence of biochemical events that lead to thrombosis of grafts is used as a guideline to describe possible counteracting prosthetic surface interventions in each separate phase of the process.

Chapter 1. Defining the Chain of Events

Introduction

The use of prosthetic grafts for repair of the arterial system is one of the major advancements in modern vascular surgery. Primarily consisting of polyester or expanded polytetrafluoroethylene (ePTFE), these grafts have done well as a substitute for occluded or stenosed arterial segments of large calibre, with diameters equal to aortic, iliac or femoral arteries. Ever since bypass surgery to the lower extremity was brought into practice, it is known that the use of autologous vein grafts yields patency rates exceeding those of prosthetic grafts.[1]

This is mainly because the exposure of the prosthetic graft surface to blood plasma leads to the development of a fibrinous pseudointima and to a subsequent cascade of events in the pre-existent 'native' intima.[2] This layer tends to thicken over time and causes narrowing of the luminal cross section, a process eventually leading to thrombotic occlusion with graft failure. In locations where native diameters are small, the effect of luminal narrowing is unequivocal as flow relates inversely to the fourth power of diameter.[3] As a consequence, every measure that stabilises the formation of the fibrin layer and that diminishes the proliferation of the intimal layer is desirable.

Upon any intervention in the circulatory system, flow patterns are being influenced and changed. Whether this is by an autologous graft, an *in situ* dilatation or a prosthetic graft, in all these cases the phenomenon of vascular remodelling is recognised. Because the wall of a prosthetic graft is stiff, the overall graft remodelling is limited, and neointimal encroachment is the major determinant of the luminal calibre.[4] Since this review focusses on prosthetic graft engineering, the process of intimal layer proliferation is emphasised. Separating the cascade into specific key events has led to a better understanding of this phenomenon. All these events may serve as a target for biomedical intervention.

Intimal hyperplasia

Intimal hyperplasia is a chronic structural change occurring in denuded arteries, arterialised veins and prosthetic bypass grafts. It is determined by hyperproliferation and migration of vascular smooth muscle cells (VSMCs) and is subdivided into hyperacute, acute and chronic stages.[5]

The first, hyperacute, stage is initiated by injury of an existing genuine intimal lining or by platelet aggregation in thrombogenic, non-autologous graft material. Proliferation of VSMCs is set in through two mechanisms: (1) damaged endothelial cells produce less inhibitors – prostacyclin, heparin sulphate, nitric oxide and natriuretic peptides – to VSMC proliferation and 2) thrombocytes themselves release heparinolytic enzymes. An increase occurs in the release of growth-stimulating factors such as fibroblast growth factor 2 (FGF2) and platelet-derived growth factor A (PDGF-A). In addition, angiotensin II, catecholamines and thrombin, all

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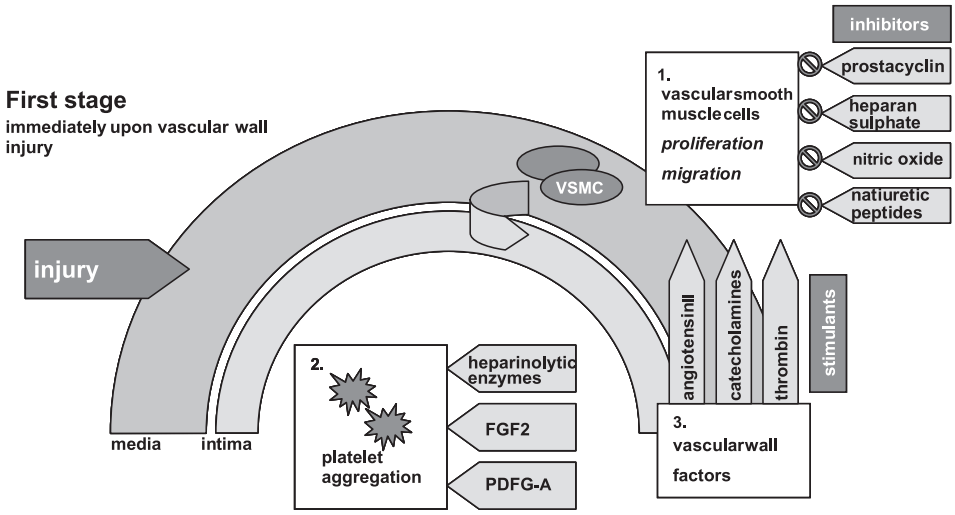

Figure 1. Hyperacute first stage of intimal hyperplasia formation.

released upon injury, also serve as stimulants in the proliferation of VSMCs (Fig. 1).

The second, acute, stage is characterised by the organisation of the thrombus, endothelial cell ingrowth and, again, the release of growth factors. In this stage, hours to weeks after injury, the integrity of the extracellular matrix is affected, which stimulates VSMC migration from the media to the intima. Both tissue-type and urokinase-type plasminogen activator are involved in this reaction. These agents activate matrix metalloproteases, further degrading the extracellular matrix (Fig. 2).[6]

In the third and final stage of intimal hyperplasia, new extracellular matrix is synthesised, a process that may continue for months after the initial lesion. In this stage, transforming growth factor β (TGF-β) and PDGF are the main stimulating factors.[7] Simultaneously, VSMC proliferation and migration, triggered in the second stage, continue mediated by insulin-like growth factor (IGF-1), TGF-β, thrombin and interleukin-1 (IL-1).[8] Together, the extracellular matrix synthesis and VSMC proliferation lead to definitive intimal expansion (Fig. 3).

The behaviour of prosthetic grafts in relation to intimal hyperplasia

Because of the allogeneic properties of prosthetic graft materials, additional effects to those described above contribute to the process of intimal hyperplasia. Several steps may be perceived: (1) foreign-body reaction leads to an inflammatory reaction activating macrophages which leads to newly excreted growth factors, (2) uncovered graft material activates platelets which also produces growth factors, (3) VSMCs proliferate as a reaction to strain due to non-physiological peri-anastomotic flow patterns, (4) turbulence itself causes injury to the endothelium of the adjacent native vessel which releases growth factors and (5) platelets adhere to regions with low shearing stress because of flow separation which, again, releases growth factors.[9] Because the aforementioned events lead to cell proliferation and extracellular matrix accumulation, they ultimately lead to vessel narrowing and graft failure.

Controlling intimal hyperplasia in prosthetic grafts

By aiming at different key events in the intimal hyperplasia cascade, the process may be down-regulated, possibly resulting in less luminal narrowing. Hypothetical controllable events are summarised in Table 1. Several molecular and pharmacologic therapies have reached an applicable status to clinical practice and will be addressed in the following section. A summary of clinically accepted pharmacological agents and their points of action is shown in Table 2.

Chapter 2. Systemic Factors Influencing Intimal Hyperplasia: Stage 1

Platelet aggregation

Controlling thrombocyte activation and subsequent aggregation has been a major issue since bypass surgery was first undertaken. Randomised clinical trials have proven benefits of acetylsalicylic

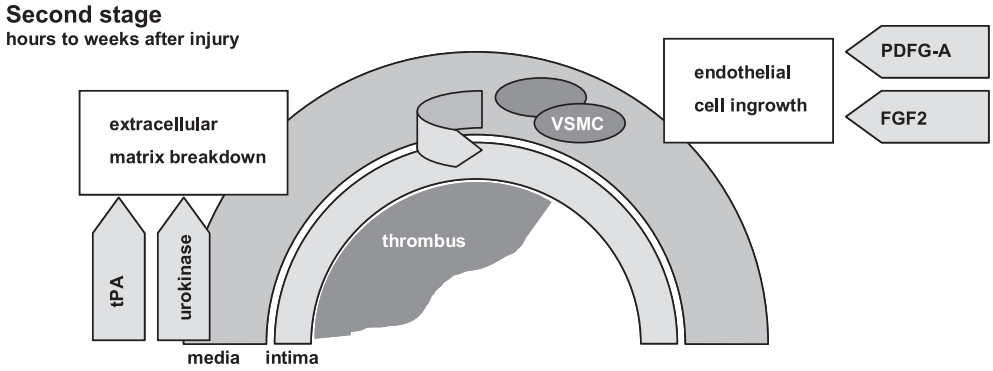

Figure 2. Acute second stage of intimal hyperplasia formation.

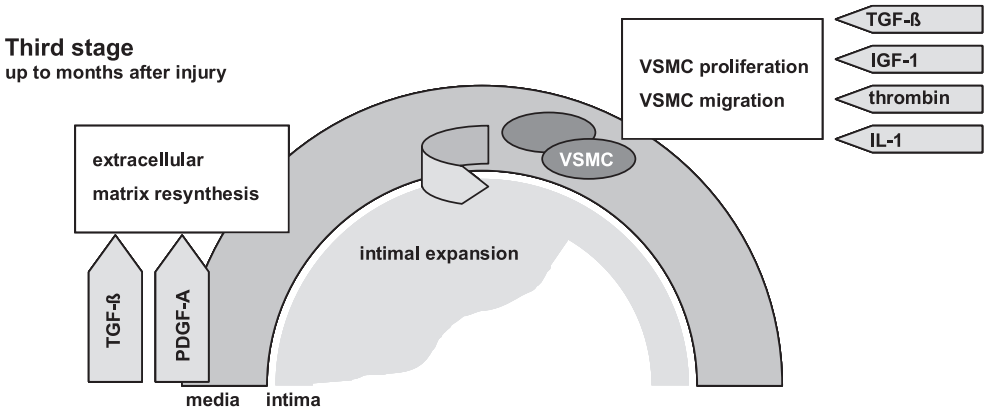

Figure 3. Chronic third stage of intimal hyperplasia formation.

acid per- and postoperatively.[10] Its point of action concentrates on irreversibly inhibiting cyclooxygenase, so as to shift the production of thromboxane A_2 – which serves as a platelet activity promotor – to the production of prostacyclin (PGI_2), which inhibits platelet activity by raising intracellular cyclic adenosine monophosphate (cAMP). The beneficial potential of the thienopyridine inhibitor clopidogrel in infrainguinal bypass surgery has recently been confirmed.[11]

Endothelial surface inhibitors of platelet aggregation

In addition to anti-platelet drugs, platelet-inhibiting surface coatings may serve as an interesting solution to platelet activation by foreign-body contact.

Anti-platelet drug coating

The concept of linking anti-platelet agents to otherwise thrombogenic surfaces is very appealing. An *in vitro* study on immobilising prostacyclin and prostaglandins to albuminated surfaces demonstrated that surfaces thus modified caused negligible platelet adherence.[12] Also, impregnating prosthetic grafts with iloprost – a prostacyclin analogue – conjugating dipyridamole to non-autologous surfaces and a slow salicylic acid releasing polymer coating were investigated. Data elicited from these experiments demonstrated a dramatic decrease of *in vitro* thrombogenicity.[13] A major issue concerning all experiments with drug-eluting systems appears to be the limitation of its action, because of the difficulties in creating a stable and constant release of pharmacological agents.

Table 1
Intimal hyperplasia pathobiology and possible targets for intervention.

Process	Pathobiology	Target
Stage 1 Intimal hyperplasia	Platelet aggregation	Cyclooxygenase Glycoprotein IIb/IIIa
	Endothelial (surface) inhibitors of platelet aggregation and SMC proliferation	Prostacyclin Heparin sulphate Nitric Oxide Natriuretic peptides
	Enzymes released by platelets	Heparinolytic enzymes
	Growth stimulating factors	bFGF PDGF
	Other mediators	Anginotensin II Catecholamines Thrombin
Stage 2 Intimal hyperplasia	Extracellular matrix breakdown	Urokinase tPA Matrix metalloproteases (MMP) IGF-1 TGF-β Thrombin Interleukin-1
Stage 3 Intimal hyperplasia	Extracellular matrix synthesis Smooth muscle cell proliferation	TGF-β PDGF

Heparin coating

Intrinsic endothelial anti-thrombotic properties are mainly dependent on heparan sulphate. Therefore, coating non-endothelialised surfaces with the glycosaminoglycan heparin might mimic the physiological situation. The key point is the retention of its bioactivity, which is very much dependent on the immobilising technique. Whereas heparin-bonded polyester grafts did not show better patency rates at 5-year follow-up, a recently published study comparing heparin-bonded ePTFE grafts to conventional ePTFE grafts showed a significant reduction in the overall risk of primary graft failure.[14,15]

Nitric oxide coating

Nitric oxide has a variety of vasoprotective properties. It can inhibit platelet adherence, decrease VSMC proliferation and migration, promote endothelial regeneration and decrease leucocyte chemotaxis.[16] The development and clinical application of polymeric biomaterials that provide a localised and sustained production of nitric oxide may lead to reduction of thrombosis and restenosis following vascular grafting of endovascular procedures. The use of nitric oxide donor molecules that were covalently incorporated into photopolymerised polyethylene glycol hydrogels proved to be effective.[17] Other techniques to incorporate nitric oxide donors into the polymer include blending into the polymer after ion-pairing and by simple dispersion within the polymer matrix. Although each approach differs in terms of nitric oxide release rates, mechanism and location, the release is maintained for 10–72 h. The biomedical application of nitric oxide releasing or generating polymers as a coating shows great promise as it may lead to a new generation of medical devices with superior biocompatibility. The impact that nitric oxide exerts on the inflammatory response to vascular injury was recognised in diabetic rats, where a heightened inflammatory response was associated with enhanced proliferative activity and with greater neointima formation. It was indicated that augmented inflammatory response and oxidative stress could be reversed by increasing nitric oxide bioavailability.[18]

Table 2
Generic names of medication therapy, brand names, availability, point of action and feasibility of incorporating in synthetic surfaces.

Generic name	Brand name	FDA approval	Point of action	Graft incorporation
Rosuvastatin, pravastatin	Crestor®, Selektin®	Yes	Inhibition of VSMC migration by impairing PDGF	Unknown
Flavoperidol	Alvocidib	Yes	Inhibition of VSMC growth by inhibition of bFGF	Unknown
Rapamycin	Sirolimus®	Yes	Inhibition of VSMC migration by inhibition of IGF-1 Inhibition of endothelial cell proliferation by inhibition of bFGF	Yes, collagen matrix
Paclitaxel	Taxol®	Yes	Inhibition of VSMC and endothelial cell proliferation and migration by preventing DNA-synthesis initiated by growth factors	Yes, collagen matrix
Heparin	–	Yes	Inhibition of VSMC growth and proliferation by indirect thrombin inhibition	Yes, collagen matrix
Nitric oxide	–	Yes	Inhibits vascular smooth muscle growth, platelet aggregation, and leukocyte adhesion to the endothelium	Yes, incorporation into photopolymerized polyethylene glycol hydrogels
Dexamethasone	–	Yes	Multiple points of action; mainly anti-inflammatory effects	Yes, suspension in lactic acid matrix or impregnation in polymer matrix
Acetylsalicylic acid	Aspirin	Yes	Inhibition of platelet activity by raising cAMP activity	Yes, polymer matrix
Ticlopidine	Ticlid®	Yes	Decreasing platelet activity and aggregation, no effect on IH	No
Clopidogrel	Plavix®	Yes	Decreasing platelet activity and aggregation, no effect on IH	No
Iloprost	Ilomedine®	Yes	Raises intracellular cAMP and decreases platelet aggregation	Unknown
Ramipril	Tritace®	Yes	Inhibits conversion to angiotensin II	No
Troglitazone	Resulin®	Yes	Inhibits PDGF, IGF-1 and bFGF	No
Argatroban	–	Yes	Direct thrombin inhibition	No
Lepirudine	Refludan®	Yes	Direct thrombin inhibition	No
Tranilast	–	Yes	Inhibition of proliferation and migration of VSMC, mechanism not fully revealed	No
Abciximab	Reopro®	Yes	Decreasing platelet activity and aggregation, probably also effect on SMC proliferation and migration	Yes
Celiprolol	Dilanorm®	Yes	Increasing nitric oxide production, reducing intimal hyperplasia	No

Natriuretic peptide coating

C-type natriuretic peptide has strong vasorelaxant properties. It appears to be an important factor regulating vascular tone. In humans, a strong expression of natriuretic peptide receptors in neointimal VSMCs has been confirmed by analysis of post-mortem atherectomy specimens.[19] The therapeutic relevance of natriuretic peptide has yet to be determined, but interventions that selectively modulate its production or activity may be of therapeutic benefit.

Enzymes released by platelets and growth-stimulating factors

Platelets are intensely involved in the first stage of intimal hyperplasia. Enzymes that are released from platelets at the site of vascular injury comprise growth-stimulating factors. Basic fibroblast growth factor (FGF2) has been shown to play an instrumental role in the cascade of events leading to restenosis. Release of heparanase and platelet factor-4 (PF4) by activated platelets liberates FGF2 from the extracellular matrix of VSMCs. FGF2 has been determined to be an important smooth muscle cell mitogen. Treatment with intravenous FGF2-neutralising antibodies significantly decreased post-injury VSMC proliferation.[20]

Another growth factor playing an important role in the early events following vascular injury is PDGF. PDGF is a mitogen and chemoattractant for VSMCs *in vitro* but induces only minimal increases in medial VSMC proliferation following vascular injury in the rat carotid artery.[21] Its main action is centred on the enhancement of intimal thickening by promoting the migration of VSMCs from the media to the intima rather than stimulating their proliferation. Since its action is dependent on luminal factors, the use of barrier agents, precluding blood and foreign-body contact, may limit the cascade leading to intimal hyperplasia.

Other mediators

The coagulation protein thrombin (activated Factor II) is a serine protease that converts soluble fibrinogen into insoluble strands of fibrin, as well as catalysing many other coagulation-related reactions. It functions as a key trigger of thrombosis and contributes to structural changes in the arterial wall that promote narrowing and clotting.[22] As the mechanisms by which thrombin leads to intimal thickening are well understood, the idea of counteracting its actions by medical intervention is tempting, since many agents exist that inhibit the effects of thrombin. Direct thrombin inhibitors are clinically used as anticoagulants. Other thrombin inhibitors recently investigated are argatroban, melagatran, dabigatran, bivalirudin and the recombinant hirudins including lepirudin and desirudin.[23]

Interfering in the renin–angiotensin cascade also affects the process of intimal hyperplasia. Blocking of angiotensin II type 1 receptors attenuates neointimal formation. This is due to the interaction between the renin–angiotensin system and the homing process of VSMCs upon arterial wall injury. While the exact mechanism for this interaction is not yet fully understood, the effects of angiotensin-converting enzyme inhibiting pharmaceuticals such as ramipril and elanapril on intimal hyperplasia have been tested in an animal model.[24] Application of these drugs, either by direct administration or indirectly by the use of drug-eluting stent grafts, seems attractive.

The process of VSMC proliferation, hypertrophy and migration is also stimulated by catecholamines, through stimulation of α_1-adrenoreceptors.[25] It is suggested that catecholamines may contribute to excessive growth of vascular wall cells in vascular diseases and injury after surgical procedures. Moreover, Hattori and co-workers demonstrated that chronic administration of the β-adrenergic blocker celiprolol inhibits vein graft intimal hyperplasia through suppression of proliferative activity in the neointima.[26]

Platelet glycoprotein IIb/IIIa inhibitors such as abciximab have shown to be effective in reducing thrombotic events in patients undergoing coronary interventions and with acute coronary syndromes.[27] They affect platelet function by occupying the fibrinogen-binding site on the platelet surface, thus preventing cross-linking of platelets by fibrinogen during thrombus formation induced by plaque disruption and rupture. In this manner, abciximab is active in inhibiting platelet aggregation and VSMC

migration and appeared to significantly reduce the level of PDGF expression in vessel lumens and neointimal VSMCs after angioplasty. Clinical therapeutic benefit has been tested in coronary stenting practice, showing a potential therapeutic benefit in preventing in-stent stenoses using abciximab-coated stent material.[28]

Chapter 3. Factors Influencing Intimal Hyperplasia: Stage 2

Extracellular matrix breakdown

The extracellular matrix includes the interstitial matrix, the inner elastic lamina and the basement membrane. The interstitial matrix consists of fibrous proteins and glycosaminoglycans, produced by resident VSMCs. It can vary in its composition by adapting to different stimuli. In healthy tissue, the matrix proteins are stable and have a slow turnover rate. In the early response after vascular wall injury, the matrix is affected by serine proteinases. Later, rebuilding of the extracellular matrix takes place, which is merged with VSMC proliferation and migration, leading to vascular wall thickening. Matrix degradation is facilitated by matrix metalloproteases (MMPs). Activation of MMP production induced by injury is initiated by the serine proteinase tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (urokinase) synthesised by vascular endothelial and VSMCs. Drugs or agents that control production of these mediators may play a role in attenuating this phase of intimal hyperplasia.

Lijnen and co-workers studied the effect of high-dose urokinase in injured murine arteries.[29] They found that reduced activity of some MMPs correlated with protection from neointimal formation and from breakdown of medial lamellar matrix. Although mechanisms in human vascular disease appear to be more complex, interfering in MMP and plasminogen activating agent production seems attractive. Long-term effects of treatment with thrombolytic agents in atherosclerotic cardiovascular diseases remain to be defined.

Chapter 4. Factors Influencing Intimal Hyperplasia: Stage 3

Extracellular matrix synthesis

The plasminogen activator system not only participates in extracellular matrix breakdown, but also plays a key role in modulating haemostasis, thrombosis and several other biological processes.[30] Overexpression of urokinase promotes neointima formation, which is probably due to active remodelling of extracellular matrix caused by excess plasmin. A role for urokinase in VSMC migration and neointima formation is confirmed, but not for tPA.[31] Upon vascular wall injury, monocytes are recruited to the site of injury, resulting in modulation of VSMC growth and migration. This interaction plays a central role in the development of vascular intimal thickening. Urokinase expressed by monocytes serves as a potent chemotactic factor for VSMCs and therefore might account for the acceleration of vascular remodelling.[32]

As fibroblast growth factors promote medial proliferation of VSMCs, migration of these cells to the intima is mainly promoted by endogenous or exogenous PDGF.[33] Insulin-like growth factor-1 (IGF-1), TGF-β, thrombin and IL-1 all take part in this process. IGF-1 is a mitogen that exerts its effects through specific receptors located on the cell membrane and promotes the multiplication of VSMCs in culture. Blocking IGF-1-mediated phosphorylation of the IGF-1 receptor in VSMCs inhibits their replication, and subsequently attenuates intimal hyperplasia after balloon injury of rat carotid arteries.[34] PDGF and TGF-β are potent VSMC mitogens *in vitro* and induce VSMC chemotaxis. Their receptors belong to a family of growth factor receptors, each sharing the common feature of activation of tyrosine kinase upon binding of growth factors. Somatostatin – a growth-inhibitory peptide found throughout the body – inhibits the stimulatory effects of selected growth factors by activating specific protein tyrosine phosphatases. Clinical use of these findings has been suggested by the use of somatostatin analogues in reducing restenosis after coronary artery interventions.[35]

Other conventional, systemically delivered drugs have been shown to inhibit VSMC proliferation and migration. Of these, troglitazone appeared to reduce neointimal formation in patients with noninsulin-dependent diabetes mellitus receiving coronary stent implantation, whereas tranilast reduced in-stent restenosis in the porcine coronary model but appears to show no clinical benefit.[36]

Cytokines are also important agents involved in this phase of intimal neoformation as intimal hyperplasia occurs by way of inflammation-dependent mechanisms.[37] IL-1 is an inflammatory cytokine that stimulates expression of adhesion molecules and induces synthesis of other proinflammatory cytokines. Also, IL-1 acts as a chemoattractant and mitogen for VSMCs and is overexpressed at sites of active proliferation and migration of these cells at the site of injury. It has been demonstrated that IL-1 receptor gene-deficient mice tend to develop less neointima and recent studies revealed a crucial role for an IL-1 receptor antagonist in the reduction of inflammation in both intima and adventitia and inhibition of neointimal formation.[38] Although it exerts effects in many ways, dexamethasone strongly prevents neointimal growth by its anti-inflammatory effects, inhibiting leucocyte adhesion and aggregation. However, systemic side effects preclude its clinical use.[39]

Since vascular narrowing has been referred to as a central feature of chronic rejection in transplanted organs, the influence of modern immunosuppressive agents on the process of intimal expansion has been studied.[40] While VSMCs in mature, normal blood vessels exhibit a differentiated, quiescent, contractile morphology, injury induces a phenotypic modulation towards a proliferative, dedifferentiated, migratory and synthetic phenotype with up-regulated extracellular matrix synthesis, which contributes to intimal hyperplasia. The mammalian target of rapamycin (mTOR) appears to play a key role in VSMC proliferation and migration. The antiproliferative effects of rapamycin on VSMCs are attributed to an inhibition of mTOR, resulting in blocked cell-cycle progression at the $G_{1/S}$ transition.[41] Rapamycin also inhibited rat and human VSMC migration in response to PDGF, although the mechanisms by which this takes place are less clear.[42] Rapamycin-coated stents or grafts may lead to the prevention of (re-)stenosis. It is compelling to use rapamycin in graft coatings, as it may promote the maintenance of functional, quiescent VSMCs at the site of injury or anastomosis.

Along with the recently evolving potential of genetic engineering, the idea of modifying the tendency of VSMCs to proliferate by genetic interference is very appealing. By manipulating the phenotype expressed on vascular endothelial cells, the emerging cascade of intimal hyperplasia could possibly be influenced. One way to achieve this is by true genetic modification introducing a gene of interest by transfection, as has been studied in cell-seeded synthetic grafts.[43] Another compelling method to change VSMC behaviour genetically aimed at a specific molecular strategy, by intra-operative treatment of harvested vein grafts with a decoy DNA molecule in order to eliminate transcripting factor activity.[44] Although this large prospective study presented disappointing primary results, it showed that intra-operative genetic intervention to modulate the vascular injury response can be executed safely and with high surgical and scientific quality.

Chapter 5. Other Modalities

Modelling the graft's surface

Creating a graft surface less hostile to blood components by resembling autologous tissue should also be addressed here. Dardik's achievement in investigating and producing grafts lined with human endothelial cells prepared the way for the concept of artificially lining synthetic grafts with human endothelial tissue by cell seeding.[45] Synthetic vascular grafts do not spontaneously endothelialise and thus usually require some form of anticoagulation to maintain patency. Hence, endothelialisation of prosthetic implants became an attractive concept. A number of different methods of obtaining an endothelial lining of prosthetic material have since been developed. These include facilitated cell migration and seeding by using either venous or microvascular endothelial cells. Although excellent *in vitro* results were obtained with prosthetic graft seeding with endothelial progenitor cells, none of these studies reported favourable effects on the clinically relevant end points, such as intimal hyperplasia or graft patency.[46] In spite of this, manipulating the endothelium might well provide the next major advancement for therapeutic and preventive measures for cardiovascular disease.

Separating blood components from a potential thrombogenic surface using artificially created layers may serve as another way to create an interface less liable to the initiation of thrombogenic reactions upon implantation. It has been demonstrated that 20-micron-thick hydrogel barriers adhering firmly to the arterial wall block thrombus deposition after deliberate injury to carotid arteries.[47] If these nonthrombogenic hydrogel barriers were to be applied to the luminal surface of a prosthetic vascular graft, this would result in the reduction of blood contact and, as such, might reduce extracellular matrix proliferation and migration after prosthetic vascular graft bypass surgery.

Modelling flow patterns

Haemodynamic factors contribute to changes in the blood vessel wall. Altered haemodynamic forces are crucial for the remodelling of vein grafts and both low- and high-flow conditions may serve as a trigger for developing intimal hyperplasia.[48] Atherosclerotic plaques, intimal hyperplasia after angioplasty and vein graft thickening are all increased in areas of low shear. Graft stenosis due to intimal hyperplasia occurs predominantly in anastomotic areas, where disturbed flow patterns and low shear stress lead to vessel wall thickening. Both *in vitro* and *in vivo* studies have shown that a large number of growth factors are regulated by shear stress, of which PDGF, FGF2 and TGF-β have been pointed out as the most important mediators.[49]

To prevent disadvantageous flow patterns at the anastomosis, the application of venous cuffs or patches evolved to ensure a more gradual transition from graft to native vessel. As an alternative, precuffed bypass grafts have been designed. In peripheral bypass graft surgery, a randomised clinical trial showed similar patency results for precuffed grafts and PTFE grafts with vein cuff.[50] Another, more recently published study addressed the use of a vein collar for the distal anastomosis of below-knee femoropopliteal and femorodistal grafts but failed to show significant differences in primary and secondary patency or limb salvage, with or without a vein collar, respectively.[51]

Chapter 6. Conclusion

As scientific boundaries are shifting and surgical techniques are refined, new treatment modalities come within reach. Understanding the principles of graft failure and elucidating the biological events responsible are of paramount importance. Bioscience and molecular chemical engineering have converged, aiming at the creation of a durable, nonthrombogenic, biocompatible, infinitely available and, thus, practically ideal synthetic bypass graft material.

Ethical Approval

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None.

Conflict of Interest

None.

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