Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists

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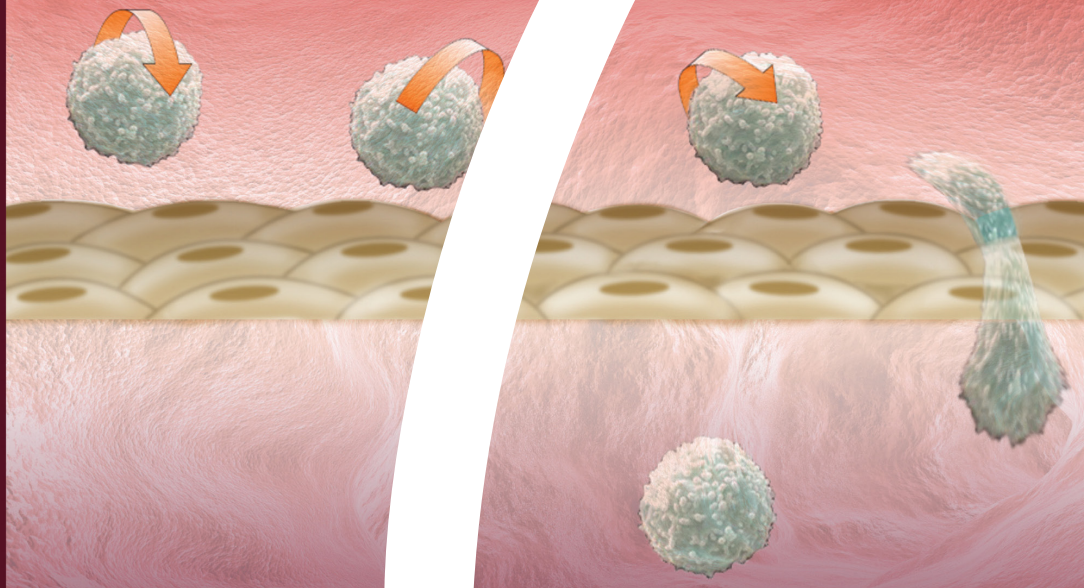

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Mechanisms of Vascular Disease

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A Reference Book for Vascular Specialists

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Abbreviation List

a1-PI	a1-protease inhibitor
5-HT	5-Hydroxytryptamine/Serotonin
AAA	Abdominal aortic aneurysm
AAS	Acute aortic syndrome
AAV	Adeno-associated viruses
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ACS	Abdominal compartment syndrome
ACTH	Adrenocorticotropic hormone
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
ADP	Adenosine diphosphate
AIDS	Acquired immune deficiency syndrome
ALI	Acute lung injury
AMP	Adenosine monophosphate
AMPA	α-amino-3 hydroxy-5-methylisoxazole
ANA	Anti-nuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
AOD	Aortic occlusive disease
AP1	Activated protein 1
APC	Activated protein C
APC	Antigen presenting cell
APLAS	Antiphospholipid antibody syndrome
ApoAI	Apolipoprotein AI
ApoE	Apolipoprotein E
APS	Antiphospholipid antibody syndrome
APTT	Activated partial thromboplastin time

ARDS	Acute respiratory distress syndrome
AT	Antithrombin
ATP	Adenosine triphosphate
AVP	Ambulatory venous thrombosis
β2-GPI	β2-glycoprotein Ib
bFGF	Basic fibroblast growth factor
BKCa	Large conductance calcium activated potassium channel
BMPs	Bone morphogenetic proteins
BMS	Bare metal stent
CAD	Coronary artery disease
CaM	Calmodulin
CAM	Cell adhesion molecule
cAMP	Cyclic adenosine monophosphate
CCK	Cholecystokinin
cGMP	Cyclic guanine monophosphate
CD	Cluster of differentiation
CD40L	Cluster of differentiation 40 ligand
CEA	Carotid endarterectomy
CETP	Cholesteryl ester transfer protein
CFD	Computational fluid dynamics
CG	Cationized gelatin
CGRP	Calcitonic gene regulated peptide
CHD	Coronary heart disease
CI	Confidence interval
CIMT	Carotid intimal-media thickness
c-JNK	c-Jun N-terminal kinase
CK-MB	Creatinine kinase (Myocardial specific)
CNCP	Chronic noncancer pain
cNOS	Constitutive nitric oxygen synthase enzyme
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CROW	Charcot restraint orthotic walker
CRRT	Continuous renal replacement therapy

CRP	C-reactive protein
CRPS	Complex regional pain syndromes
CT	Computational tomography
CTA	Computed tomographic angiography
CTD	Connective tissue disorders
CTGF	Connective tissue growth factor
CYP	Cytochrome P450
CVD	Cardiovascular disease
CVI	Chronic venous insufficiency
DAG	Diacylglycerol
DES	Drug-eluting stent
DRG	Dorsal root ganglion
DNA	Deoxyribonucleic acid
DSA	Digital subtraction arteriography
DTS	Dense tubular system
DVT	Deep vein thrombosis
EC	Endothelial cell
ECM	Extracellular matrix
EDCF	Endothelium-derived contracting factor
EDH	Endothelium-dependent hyperpolarisation
EDS	Ehlers-Danlos syndrome
EET	Epoxyeicosatrienoic acids
ELAM-1	Endothelial-leukocyte adhesion molecule-1
ELG	Endoluminal grafts
ELISA	Enzyme linked immunosorbent assay
E_K	Equilibrium potential
E_M	Membrane potential
eNOS	Endothelial nitric oxide synthase enzyme
EPC	Endothelial progenitor cells
EPCR	Endothelial protein C receptor
ePTFE	Expanded polytetrafluoroethylene
ERK	Extracellular signal-regulated kinase
ESR	Erythrocyte sedimentation rate

ET	Essential thrombocytosis
ET-1	Endothelin 1
EVAR	Endovascular aortic aneurysm repair
EVLA	Endovenous LASER ablation
FDA	Food and drug administration
FDPs	Fibrin degradation products (soluble)
FGF	Fibroblast growth factor
FGF-2	Fibroblast growth factor 2
FMN	Flavin mononucleotide
FVL	Factor V Leiden
GABA	Gamma-aminobutyric acid
GABA B	Gamma-aminobutyric acid subtype B
G-CSF	Granulocyte colony stimulating factor
GMCSF	Granulocyte-macrophage colony stimulating factor
GP	Glycoprotein
GPCR	G-protein coupled receptor
GSV	Great saphenous vein
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HIF	Hypoxia inducible factor
HIT	Heparin induced thrombocytopenia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG Co-A	Hydroxymethylglutaryl coenzyme-A
HMW	High molecular weight
HPETE	Hydroperoxyeicosatetraenoic acid
HETE	Hydroxyeicosatetraenoic acids
HR	Hazard ratio
hsCRP	High-sensitive C-reactive protein
HSP	Heat shock protein
HUV	Human umbilical vein
IAH	Intra-abdominal hypertension

IAP	Intra-abdominal pressure
IAPP	Intra-abdominal perfusion pressure
ICAM-1	Inter-cellular adhesion molecule-1
ICAM-2	Inter-cellular adhesion molecule-2
ICP	Intra-compartmental pressure
ICU	Intensive care unit
IFN	Interferon
IGF-1	Insulin-like growth factor-1
IHD	Ischemic heart disease
IL	Interleukin
IL-1	Interleukin-1
IL-1α	Interleukin-1 alpha
IL1-β	Interleukin-1 beta
IL-6	Interleukin-6
IL-8	Interleukin-8
ILT	Intraluminal thrombus
IKCa	Intermediate conductance calcium-activated potassium channels
IMH	Intramural haematoma
IMP	Inosine monophosphate
iNOS	Inducible nitric oxide synthase enzyme
IP(3)	1,4,5-inositol triphosphate
IRI	Ischemia reperfusion injury
IVIG	Intravenous pooled immunoglobulin
IVUS	Intravascular ultrasound
KGF	Keratinocyte growth factor
KGF-2	Keratinocyte growth factor-2
LAP	Latency associated peptide
LCS	Limb compartment syndrome
LDL	Low density lipoprotein
LDS	Loeys-Dietz syndrome
LLC	Large latent complex
LEC	Lymphatic endothelial cells

LFA-1	Lymphocyte function-associated antigen-1
LO	Lipoxygenase
LOX	Lysyl oxidase
LOPS	Loss of protective sensation
LPA	Lysophosphatidic acid
LPS	Lipopolysaccharide
LTA	Lipoteichoic acid
LTGFBP	Latent TGF binding protein
MAC-1	Macrophage-1 antigen
MAPK	Mitogen activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage-colony stimulating factor
MFS	Marfan syndrome
MHC	Major histocompatibility
MI	Myocardial infarction
MIP-1	Macrophage inflammatory protein-1
MLC_{20}	Myosin light $chain_{20}$
MLCK	Myosin light chain kinase
MLCP	Myosin light chain phosphatase
MMP	Matrix metalloproteinase
MODS	Multiple organ dysfunction syndrome
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MRSA	Methicillin resistant *Staphylococcus aureus*
MRSE	Methicillin resistant *Staphylococcus epidermidis*
MRTA	Magnetic resonance tomographic angiography
MTHFR	Methylenetetrahydrofolate reductase
MT-MMP	Membrane-type MMP
MVPS	Mitral valve prolapse syndrome
NADPH	Nicotinamide adenine dinucleotide phosphate
NGF	Nerve growth factor

NFκB	Nuclear factor kappa B
NiTi	Nitinol
NJP	Non-junctional perforators
NMDA	N-methyl-D-aspartate
NNH	Number needed to harm
NNT	Number needed to treat
NO	Nitric oxide
NOS	Nitric oxide synthase enzyme
NSAID	Non-steroidal anti-inflammatory drug
NV	Neovascularisation
OCP	Oestrogen/progesterone contraceptive pill
OPN	Osteopontin
OPG	Osteoprotegerin
OR	Odds ratio
OxLDL	Oxidised low density lipoprotein
PAD	Peripheral arterial disease
PAF	Platelet activating factor
PAI	Plasminogen activator inhibitor
PAI-1	Plasminogen activator inhibitor-1
PAR	Protease activated receptor
PAR-1	Protease activated receptor-1
PAR-4	Protease activated receptor-4
PAU	Penetrating aortic ulcer
PC	Protein C
PCA	Poly (carbonate-urea) urethane
PCI	Percutaneous coronary intervention (angioplasty)
PCWP	Pulmonary capillary wedge pressure
PDGF	Platelet-derived growth factor
PDGFβ	Platelet-derived growth factor-β
PDS	Polydioxanone
PECAM-1	Platelet-endothelial cell adhesion molecule-1
PEDF	Pigment epithelium-derived factor
PES	Paclitaxel-eluting stent

PET	Positron emission tomography
PF4	Platelet factor 4
PGI_2	Prostacyclin
PGG_2	Prostaglandin G_2
PGH_2	Prostaglandin H_2
$PGEI_2/PGI_2$	Prostaglandin I_2
PGN	Peptidoglycan
PHN	Postherpetic neuropathy
PHZ	Para-anastomotic hyper-compliant zone
PI3K	Phosphatidylinositol 3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PLC	Phospholipase C
PLOD	Procollagen lysyl hydroxylase
PMCA	Plasma membrane Ca^{2+} APTases
PMN	Polymorphonuclear leukocyte
POSS	Polyhedral oligomeric silsesquioxanes
PPAR	Peroxisomal proliferation activating receptor
PPI	Proton pump inhibitor
PRV	Polycythaemia rubra vera
PS	Protein S
PSGL-1	P-selectin glycoprotein ligand-1
PT	Prothombin time
PTCA	Percutaneous coronary angioplasty
PTFE	Polytetrafluoroethylene
PTS	Post-thrombotic syndrome
PUFA	Polyunsaturated fatty acid
PVI	Primary valvular incompetence
rAAA	Ruptured AAA
Rac	Ras activated cell adhesion molecule
RANTES	Regulated upon activation, normal T cell expressed and secreted
RAS	Renin angiotensin system
RCT	Randomised controlled trial

RF	Rheumatoid factor
RFA	Radiofrequency ablation
rhAPC	Recombinant human activated protein C
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RR	Relative risk
RSD	Reflex sympathetic dystrophy
S1P	Sphingosine-1-phosphate
SAPK	Stress-activated protein kinase
SCF	Stem cell factor
SCS	Spinal cord stimulation
ScvO2	Superior vena cava venous oxygen saturation
SDF-1	Stromal-cell-derived factor-1
SERCA	Sarco/endoplasmic reticulum CaATPases
SEP	Serum elastin peptides
SES	Sirolimus-eluting stent
SEPS	Subfascial endoscopic perforator surgery
SFA	Superficial femoral artery
SFJ	Sapheno-femoral junction
SIRS	Systemic inflammatory response syndrome
SKCa	Small conductance calcium-activated potassium channels
SLE	Systemic lupus erythematosus
SMA	Smooth muscle alpha actin
SMC	Smooth muscle cell
SMP	Sympathetically maintained pain
SNARE	Soluble N-ethylmaleimide-sensitive factor activating protein receptors
SNP	Single nucleotide polymorphisms
SNRI	Serotonin/Noradrenaline reuptake inhibitors
SPJ	Sapheno-popliteal junction
SPP	Skin perfusion pressure
SR	Sarcoplasmic reticulum
SSRIs	Selective serotonin re-uptake inhibitors
SSV	Small saphenous vein

SVT	Superficial thrombophlebitis
STIM1	Stromal interacting molecule 1
TαCE	TNFα converting enzyme
TAAD	Thoracic aortic aneurysm disease
TAD	Thoracic aortic dissection
TAFI	Thrombin-activatable fibrinolysis inhibitor
Tc-99 MDP	Technetium-99 methylene diphosphonate
TCA	Tricyclic antidepressant
TCC	Total contact cast
TCR	T-cell receptor
TENS	Transcutaneous electrical nerve stimulation
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TGF	Transforming growth factor
TGF-α	Transforming growth factor-alpha
TGF-β	Transforming growth factor-beta
TGL	Triglycerides
Th	T helper
TIA	Transient ischemic attack
TIMP	Tissue inhibitors of metalloproteinase
TLR	Toll-like receptors
TNF	Tumour necrosis factor
TNF-α	Tumour necrosis factor-alpha
tPA	Tissue-type plasminogen activator
TRP	Transient receptor potential
TRPC	Transmembrane receptor potential canonical
TRPV1	Transmembrane receptor potential Vanilloid-type
TXA2	Thromboxane A2
uPA	Urokinase
UT	University of Texas
VCAM	Vascular cell adhesion molecule
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor

VEGF-R	Vascular endothelial growth factor receptor
VIP	Vasoactive intestinal peptide
VLA-1	Very late activating antigen-1
VOCC	Voltage operated calcium channels
VPT	Vibratory perception threshold
VSMC	Vascular smooth muscle cells
VTE	Venous thromboembolism
VV	Varicose veins
vWF	von Willebrand factor
XO	Xanthine oxidase

7 • Biology of Restenosis and Targets for Intervention

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INTRODUCTION

Restenosis is usually defined as a re-narrowing of the arterial lumen occurring after a vascular intervention intended to treat ischemic lesions. This loss of lumen area results from the injury caused by all forms of vascular intervention, including direct repair (patch angioplasty, endarterectomy) and intraluminal approaches (balloon angioplasty, atherectomy, stent angioplasty). While there are clear differences between arteries and veins (review in[1]), this review will also include discussion of stenosis after vein bypass grafting or creation of arteriovenous fistula dialysis access because stenosis in these cases also results from injury.

Lumen enlargement after angioplasty or stenting is the result of a combination of plaque reduction (compression and embolization), plaque redistribution within or outside the lesion area, and vessel expansion (see review[2]). Failure occurs at early times because of technical problems and thrombosis (e.g. small diameter vein graft, limited outflow, or hypercoagulability) and later times (1-18 months) primarily because of injury-induced scarring. At much later times (> 18 months), failure primarily results from the ongoing atherosclerotic process. Although restenosis occurs within the context of atherosclerosis, the clinical features and genetic control of atherosclerosis and restenosis are different.[3] Atherosclerosis develops slowly over decades,[4] while restenosis occurs within months to years.[5]

The costs of restenosis are considerable, since greater than 20% of all interventions fail because of restenosis. In the U.S. alone, it is estimated that as many as 200,000 cases of drug eluting stent (DES) restenosis occur every year (see review[6]). The goal of research in this area is to modify vascular healing so that injury is repaired without lumenal narrowing. The objectives of this chapter are to review mechanisms of restenosis and current and potential molecular targets to prevent restenotic lesions.

MECHANISMS OF RESTENOSIS

Restenosis results from a combination of elastic recoil, thrombosis, remodelling and intimal hyperplasia. Three decades ago the prevailing view was that restenosis was primarily a problem of intimal hyperplasia caused by migration of SMCs from the media to the intima followed by excessive growth. Two decades ago a role for remodelling was confirmed and more recently a possible role for progenitor/stem cells has gained ground. Because recoil is not an issue after stenting

and is a mechanical property of elastic layers of the artery, we will focus on the roles of thrombosis, remodelling and intimal hyperplasia, which contribute to varying degrees depending on the intervention employed (e.g. angioplasty vs. stenting).

Thrombosis

Thrombosis may occur after vascular intervention because of damage to the endothelium and possible intimal and medial dissection. Mechanisms of this process are presented more fully in Chapter 10 on the haemostatic system. Briefly, exposure of underlying tissue factor to blood causes thrombin and fibrin generation, which along with platelets may lead to thrombotic occlusion.[7] Adherence of platelets is mediated by receptors such as the integrin, IIb/IIIa. Aggregation of platelets causes the release of numerous factors, including thromboxane A2, ADP, serotonin, and matrix metalloproteinases 2 and 9, that further stimulate platelet adherence and/or aggregation.[5,8] Platelets also release a variety of growth and chemotactic factors.[8] Thrombus can act as a scaffold through which SMCs migrate and both synthesize and degrade extracellular matrix components, thus reorganizing the thrombus. While anti-platelet therapy largely prevents acute thrombosis after vascular intervention, late thrombosis in DES remains of concern prompting prolonged anti-platelet therapy.[6] Even in the absence of thrombotic occlusion, there is considerable evidence of a relationship between the early thrombotic response and the later development of restenosis.[9] Anti-platelet therapy, particularly inhibitors of IIb/IIIa in both animals and humans has demonstrated the importance of platelets to the restenotic process.[8,10-13] For example, knockout of P2Y12, the ADP receptor on platelets, or its blockade using clopidogrel inhibits neointimal formation after arterial injury.[14] Fibrin deposition on stent struts and decreased heparin cofactor II, a thrombin inhibitor, are both associated with in-stent restenosis[15,16] (Table 7.1). Larger platelets, which contain more prothrombotic material per unit volume, are also associated with restenosis.[17] However, the clinical relevance of these findings has not been fully evaluated. For example, low platelet responsiveness to clopidogrel, a predictor of thrombotic complications, is not a predictor of DES restenosis.[18]

Remodelling

Remodelling refers to a change in the total area of the vessel (generally measured as a loss of the area within the external elastic lamina) that affects lumenal dimensions of the blood vessel not attributable to vasospasm, vasodilation, or changes in wall area. Remodelling can be favorable (outward, positive, compensatory, or adaptive) or unfavorable (inward, negative, or maladaptive). Vascular remodelling occurs normally in response to changes in blood flow, wall mass, or wall tension (as during normal development, atherosclerotic lesion development, or hypertension) as an adaptation to maintain normal blood flow (see review[19]). Post-angioplasty, arteries show further gains in lumen area between 1 day and 1 month after angioplasty, but then lose some vessel area thereafter with restenotic arteries showing a greater loss than non-restenotic arteries. Negative remodelling contributes more than intimal hyperplasia to restenosis after coronary and peripheral artery angioplasty[5,96] and in vein graft stenosis,[1,97,98] but in rigid artificial grafts and stented arteries intimal hyperplasia is the primary mechanism of restenosis.[5]

The regulation of arterial remodelling is poorly understood, but since wall tension and shear stress are normally regulated

TABLE 7.1: Recent Studies of Biologically Relevant, Non-technical Factors Implicated in Restenosis

Factor (+ if positively, - if negatively associated)	Independent Predictor of restenosis after:	Not an Independent Predictor of restenosis after:	Patients, N	Citation
Patient Characteristics				
End stage renal disease **(+)**	Fem-pop BMS		511	[20]
	Coronary DES (recurrent restenosis)		990	[21]
	Coronary BMS		34	[22]
Diabetes **(+)**	Carotid endarterectomy		243	[23]
		Carotid endarterectomy	308	[24]
	Lower extremity angioplasty		40	[25]
	Angioplasty of AV fistula		140	[26]
		Renal artery stent/ angioplasty	91	[27]
	Coronary SES or PES		545	[28]
	Coronary SES		1312	[29]
	Coronary stent		3104	[30]
	SES for coronary BMS restenosis		244	[31]
		Coronary BMS	345	[32]
		Coronary BMS and DES	274	[33]
		Coronary angioplasty	92	[34]
		Coronary BMS	109	[35]
Vascular Characteristics				
Echolucent femoral (non-target) lesion **(+)**	Carotid endarterectomy		321	[36]
Echolucent plaque **(+)**	Carotid endarterectomy		308	[24]
	Coronary angioplasty		92	[34]
Collagen content **(+)**	Femoral endarterectomy		217	[37]
Positively remodeled lesion **(+)**	Coronary BMS		85	[38]
	Coronary BMS		113	[39]

Factor (+ if positively, - if negatively associated)	Independent Predictor of restenosis after:	Not an Independent Predictor of restenosis after:	Patients, N	Citation
Decreased macrophages, lipid core in lesion **(+)**	Carotid endarterectomy		500	[40]
Atherosclerotic burden – Gensini score **(+)**	Coronary angioplasty		345	[32]
Brachial intima/media thickness	Iliac/femoral angioplasty; BMS		128	[41]
Impaired forearm reactive hyperemia **(+)**	Coronary BMS		47	[42]
	Coronary BMS DES		136	[43]
		Iliac/femoral angioplasty; BMS	128	[41]
High collateral function **(+)**	Coronary BMS		95	[44]
	Coronary angioplasty		64	[45]
	Coronary angioplasty		91	[46]
		Coronary BMS	58	[47]
SNPs and soluble factors *Growth Inhibitors and Stimulants*				
eNOS (Glu298Asp) **(+ TT)**	Coronary BMS		106	[48]
eNOS (Glu298Asp) **(+ TT)**	Coronary BMS		226	[49]
eNOS (Glu298Asp)		Coronary BMS	3104	[30]
Heme Oxygenase-1 promoter $(GT)_n$ length polymorphism **(+)**	Coronary BMS		323	[50]
		Coronary BMS	1807	[51]
p27 -838C>A **(+ CC)**	Coronary BMS		715	[52]
Nurr1 haplotype **(-)**	Coronary BMS		601	[53]
Pre-procedure Adiponectin **(-)**	Coronary BMS in end stage renal disease		71	[54]
Pre-procedure HMW adiponectin **(-)**	Infrainguinal saphenous vein graft		225	[55]

Factor (+ if positively, - if negatively associated)	**Independent Predictor of restenosis after:**	**Not an Independent Predictor of restenosis after:**	**Patients, N**	**Citation**
Change in adiponectin **(-)**	Coronary BMS and DES		32	[56]
Pre-procedure Resistin **(+)**	Infrainguinal saphenous vein graft		225	[55]
	Coronary BMS		70	[57]
Inflammation				
Pre-procedure CRP **(+)**	Angioplasty of femoral, popliteal arteries		172	[58]
		Carotid endarterectomy	64	[59]
	Coronary DES		167	[60]
		Coronary DES	134	[61]
	Coronary angioplasty and BMS		850	[62]
		Coronary angioplasty	345	[32]
		Coronary angioplasty	162	[63]
		Coronary angioplasty	168	[64]
		Coronary angioplasty	345	[65]
		Coronary angioplasty	216	[66]
	Meta-analysis of coronary angioplasty (includes [64] [66])		1062	[67]
IL-*1B–511* SNP*(T/C)* **(+ TT)**	Coronary stent (type unclear)		165	[68]
		Coronary angioplasty	171	[69]
IL-1R antagonist*2 **(-)**	Coronary angioplasty		171	[69]
Pre-procedure IL-3 **(+)**	Coronary stent (type unclear)		205	[70]
IL-6 SNP (-174 G/C) **(+ CC)**	Fem-pop angioplasty		281	[71]
IL-6 SNP (-174 G/C and -572 G/C)		Coronary BMS	3104	[30]
Pre-procedure soluble CD40 ligand **(+)**	Coronary angioplasty		70	[72]
		Coronary angioplasty	162	[63]

Factor (+ if positively, - if negatively associated)	**Independent Predictor of restenosis after:**	**Not an Independent Predictor of restenosis after:**	**Patients, N**	**Citation**
CD11b level and activation on leukocytes **(+)**	Coronary BMS		62	[73]
CD18 SNP (1323 C/T) **(+ TT)**	Coronary stent		1207	[74]
CD14 SNP (-260C/T) **(+ CC)**	Coronary BMS		3104	[30]
Change in MCP-1 blood levels **(+)**	Coronary DES BMS		32	[75]
TNFα –238G-1031T haplotype **(+)**	Coronary angioplasty		3104	[76]
TNFα release during procedure **(+)**	BMS into stenotic saphenous coronary bypass graft		18	[77]
CCL11 (Eotaxin) SNP (-1328G/A) **(+ GG)**	Coronary BMS		3104	[30]
Colony Stimulating Factor 2 SNP (Ile117Thr) **(+ Ile)**	Coronary BMS		3104	[30]
Colony Stimulating Factor 3 at 24 hours **(+)**	Coronary BMS		40	[78]
Oxidized LDL change **(+)**	Coronary BMS after acute infarction		109	[35]
Pre-procedure monocyte VEGF expression **(+)**	Coronary BMS and SES		41	[79]
$CD34^+$ cells on day 7 **(+)**	Coronary BMS		40	[78]
$CD34^+$ cells **(+)**	Coronary BMS		17	[80]
Complement/Lectin				
Mannose Binding Lectin (MBL) 2, A/A alleles **(+)**	Carotid endarterectomy		123	[81]
Pre-procedure Complement C3 **(+)**	Carotid endarterectomy		64	[82]

Factor (+ if positively, - if negatively associated)	**Independent Predictor of restenosis after:**	**Not an Independent Predictor of restenosis after:**	**Patients, N**	**Citation**
Complement C3 SNP (Arg102Gly)		Coronary BMS	3104	[30]
Pre-procedure C1-Inhibitor **(+)**	Carotid endarterectomy		64	[59]
Change in VEGF and PDGF-AB in patients with MBL2 A/A alleles **(+)**	Carotid endarterectomy		53	[83]
Vasoactivity				
Beta2 adrenergic receptor SNP (Arg16Gly) **(+ Gly)**	Coronary BMS		3104	[30]
Asymmetric dimethyl arginine **(+)**	Angioplasty of failed AV fistula in ESRD		100	[84]
Pre-procedure N-terminal Brain Natriuretic Protein **(+)**	Coronary angioplasty		345	[32]
Post-procedure N-terminal Brain Natriuretic Protein **(+)**	Coronary BMS and DES		249	[85]
Haemostatic/Fibrinolytic system				
Mean platelet volume **(+)**	Meta-analysis coronary angioplasty and stent		430	[17]
Heparin Cofactor II **(-)**	BMS in restenotic fem-pop post angioplasty		63	[16]
	Coronary BMS		134	[86]
Urokinase **(+)**	Coronary BMS		49	[87]
Other				
Pre-procedure LDL particle size **(+)**	Coronary BMS and DES		274	[33]
Lipoprotein(a) **(+)**	Coronary BMS		109	[88]
Active MMP9 **(+)**	Coronary BMS		286	[89]
MMP9 **(+)**	Coronary stent		40	[90]

Factor (+ if positively, - if negatively associated)	Independent Predictor of restenosis after:	Not an Independent Predictor of restenosis after:	Patients, N	Citation
Active MMP3 or MMP9	Coronary BMS		152	[91]
MMP2 and MMP9 **(+)**	Coronary DES		85	[92]
5A/6A MMP3 SNP **(6A+)**	Coronary BMS		344	[93]
		Coronary BMS	198	[94]
	Coronary angioplasty		287	[94]
		Coronary angioplasty	48	[95]
Pre-procedure Pregnancy-associated plasma protein A **(+)**	Coronary angioplasty		162	[63]

This table is not an inclusive list of all studies of risk factors for restenosis. Studies showing non-technical factors as independent risk factors for restenosis (i.e. angiography, duplex US) by multivariate analysis were included as were studies showing a lack of independence of these same factors.

within a narrow range in mammals (see review[19]), it must involve the transduction of the forces of shear stress and wall tension into biochemical signals leading to the breaking and reforming of ECM attachments, both matrix to matrix and cell to matrix. For example, the wall thickening that occurs in vein grafts and hypertensive arteries normalizes wall tension. A mechanoregulation model of remodelling proposed by Grinnell and colleagues, in which strain-regulated cell migration and collagen translocation can produce large scale tissue movement,[99] is relevant to both vascular and cutaneous injury, which share several features. For example, skin wounds contract as do negatively remodelling arteries, ECM changes are similar in injured skin and artery (increased biglycan and versican and less decorin), and smooth muscle actin-positive cells appear in the skin wound (myofibroblasts) and in the injured arterial adventitia. Of interest, there is a possible association between abnormal skin wound healing and restenosis.[100] Support for a mechanoregulatory model comes from observations after vascular and cutaneous injury. Releasing tension by external wrapping of arteries and by external pressure or skin flapping to skin wounds causes tissue regression through apoptosis and loss of ECM.[101-103] Detaching collagen gels embedded with SMCs so that they float releases tension and causes SMC death and inhibits ECM production.[104] Finally, increasing tension by stretching arteries ex vivo and by external skin splinting causes cell proliferation and increased tissue mass.[105-107] The tension in the cell-ECM has been shown to regulate which signaling pathways are utilized,[99] and several signaling mediators are implicated in

the regulation of remodelling. One example is NO, but while NO formed by iNOS and nNOS inhibits negative remodelling, that formed by eNOS does not influence remodelling. Whether the particular isoform of NOS or the particular cell expressing NOS is critical is not known. The P2X4 ion channel, which is needed for NO production, is also necessary for flow-mediated remodelling, as is the cytoskeletal filament, vimentin, which is a key intracellular protein in the transmission of contractile forces.[19]

The roles of the adventitial, medial, and intimal layers of the artery in remodelling are not clear though each provide significant mechanical strength to the human artery.[108] Some data suggest that adventitial fibrosis and collagen accumulation contribute to negative remodelling.[109] SMCs synthesize collagen fibrils in a manner dependent on fibronectin fiber assembly, $\alpha 2\beta 1$ integrin, and RhoA activity, as well as an intact actin cytoskeleton, which is required for tension development.[110] Of interest, blockade of fibronectin assembly or Rho kinase prevents positive arterial remodelling.[111,112] Fibronectin regulates signaling by the transcription factor NFκB,[113] which mediates $\alpha 2\beta 1$ integrin-directed SMC collagen gel contraction[114] and remodelling of vessels caused by circumferential and axial stress.[106,107,115,116]

Finally, inhibition of ECM protein cross linking by inhibition of lysyl oxidase or transglutaminase inhibits negative remodelling after angioplasty and blood flow reduction, respectively.[117,118] Thus, arterial remodelling may involve the interaction of mechanical stress with fibronectin/collagen fibrillogenesis mediated by integrin/NFκB signaling as well as ECM cross-linking. The possible roles in remodelling of MMPs and other ECM components will be discussed below (sections on matrix metalloproteinases and extracellular matrix/receptors). Finally, ongoing studies are focused on defining genetic determinants of murine flow-induced remodelling.[19]

Intimal hyperplasia

Intimal hyperplasia results from the net increase in cell number and ECM, which are dependent on rates of cellular migration, proliferation, and death and on rates of ECM synthesis and degradation, respectively. Our understanding of the underlying cellular mechanisms of intimal hyperplasia comes from animal models of vascular injury, since the ability to study the human response at the cellular and biochemical level has been limited. A variety of methods of arterial injury has been employed including a partially inflated Fogarty embolectomy catheter, loose-fitting external cuffs, endolumenal wires or nylon loops, adventitial electrical injury, complete or partial arterial ligation, and stents. Some of these methods share features of clinically used interventions (e.g. stents) while others do not (ligation; see review[119]). Despite their limitations, animal models of vascular injury have provided a general understanding of the sequence of events after injury.[120]

Sequence of Events after Injury

The sequence of events after arterial injury is illustrated in Figure 7.1. Depending on the type of injury, endothelial cells are either injured or completely removed resulting in the loss of the quiescent endothelial cell layer, which inhibits SMC proliferation and intimal hyperplasia.[121,122] Within 30 minutes of balloon injury up to 70% of medial SMCs die via apoptosis. Placement of vein grafts and stents into the arterial circulation, as well as arterial ligation, also cause apoptosis (review in[2]). Some data suggest that cell death increases intimal hyperplasia,[123-125] but SMC death by itself does not appear to cause intimal hyperplasia.[126]

Prior to the start of proliferation, SMCs

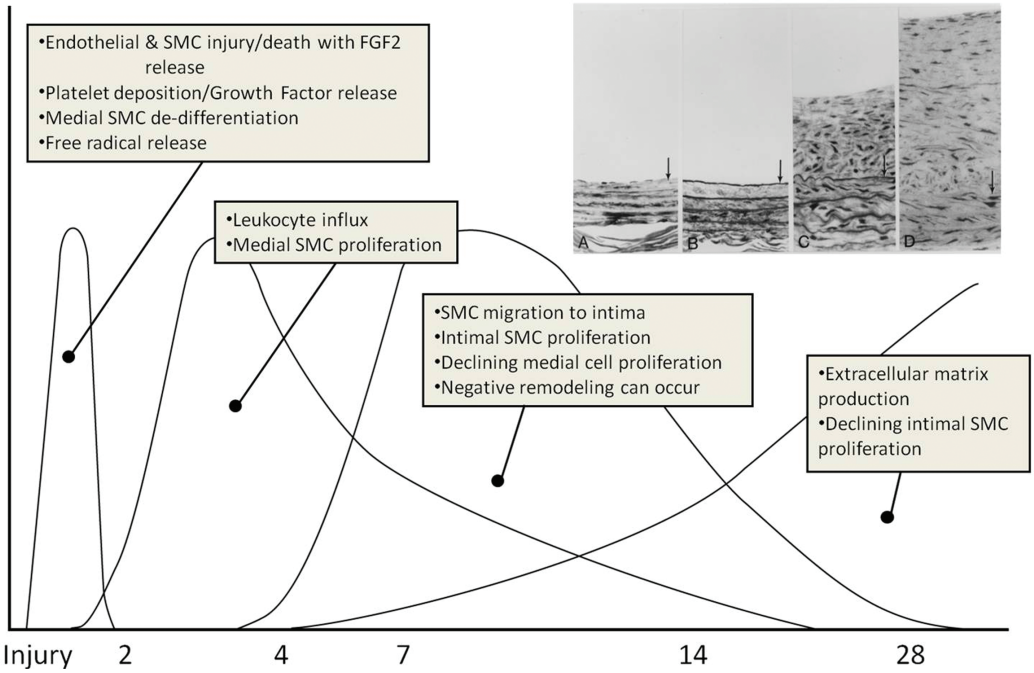

FIGURE 7.1: Sequence of events leading to intimal hyperplasia after arterial injury including histological cross-sections of injured rat carotid arteries: (a) normal vessel. Note the single layer of endothelium in the intima; (b) denuded vessel at two days. Note the loss of endothelium; (c) denuded vessel at two weeks. Intima is now markedly thickened due to smooth muscle migration and proliferation; and (d) denuded vessel at 12 weeks. Further intimal thickening has occurred. Internal elastic lamina indicated by an arrow.

in the media express high levels of SMC-specific contractile proteins, such as smooth muscle alpha actin (SMA), and are quiescent with no significant ECM production. After injury, SMCs change to a de-differentiated phenotype with SMCs expressing decreased levels of SMC-specific contractile proteins[127] and increased levels of migration, proliferation, and ECM synthesis. The regulation of this transition has been studied at the transcriptional level for markers of SMC differentiation[128] and for many years it has been assumed that expression of these genes might inhibit proliferation. Recent data supports this for SMA in that specific mutations in SMA cause SMCs to proliferate faster in vitro and cause coronary artery disease.[129]

The medial SMC proliferation rate during the first two to four days jumps from 0.06% before injury to 10-40% in the injured arteries of rats, mice, rabbits, and non-human primates (review in[2]). Adventitial proliferation begins earlier and is maintained along with medial proliferation.[130] Animal and clinical studies with stents indicate that intimal hyperplasia is generally correlated with the degree of injury.[2,15] By four weeks cell growth in the media and adventitia returns to baseline. By eight weeks, when intimal growth is maximal, growth returns to baseline in endothelialized intima, but SMCs at the luminal surface in deendothelialized areas continue to proliferate at a low rate.[131]

Migration of medial SMCs into the rat and mouse neointima occurs as early as 4 days after injury.[132,133] The role of SMC migration in human vessels remains an unknown,

because the presence of intimal SMCs in normal arteries as well as in arterial lesions makes the measurement of migration impossible by currently available methods. In addition, the long term significance of medial SMC migration is uncertain, since pharmacological inhibition of migration causes only transient inhibition of intimal hyperplasia (e.g. MMP inhibitors and heparin; see review[2]). Thus, especially when there are pre-existing intimal SMCs, the impact of medial SMC migration is not clear.

There are very little data on the rate of growth of lesions in humans as most studies report baseline and final lesion size and serial angiography after angioplasty does not differentiate between negative remodelling and intimal hyperplasia. Available data indicates that intimal growth in stents is greatest from 0-6 months with a small increase (in DES) or decrease (in BMS) between 6–24 months.[134,135] Maximal intimal hyperplasia is achieved by 2 months after arterial injury in rats, rabbits and baboons[131,136,137] and after stenting in rats.[138] Differences in the thrombotic response[139] as well as differences in rates of recovery of the endothelium[140] may explain some of this variability. Genetic differences can explain some but not all of these differences in animals as well as humans.[3,141-143]

A considerable number of risk factors for restenosis are associated with intimal hyperplasia (Table 7.1). Regarding renal failure and type 2 diabetes, while there are few studies of arterial injury in animal models of type 2 diabetes (in contrast to type 1)[144] or renal failure, increased intimal hyperplasia is observed in arterio-venous fistulas in a mouse model of renal failure and in vein grafts in a mouse model of type 2 diabetes.[145,146] In addition, SMCs obtained from type 2 diabetic patients display increased proliferative and migratory capacity in vitro compared to SMCs from non-diabetic patients.[147] A SNP of p27, which is an inhibitor of cyclin-dependent kinases and proliferation,[148] increases basal promoter activity and is associated with less restenosis.[52] Certain haplotypes of Nurr1, a transcription factor that inhibits SMC proliferation, are associated with restenosis.[53] eNOS SNPs associated with restenosis may decrease levels of NO, which is a SMC growth inhibitor as well as vasodilator,[149] Adiponectin, which inhibits SMC growth,[150] is negatively associated with restenosis. In contrast, resistin, which is positively associated with restenosis, stimulates SMC growth.[151] Finally, a role for cell proliferation in vein graft stenosis is supported by the increased proliferative capacity of cells cultured from veins of patients that develop stenosis.[152]

Several predictive factors for restenosis may be associated with decreased blood flow through the lesion (Table 7.1), which is known to increase intimal hyperplasia in animal models.[153] These factors include impaired forearm reactive hyperemia, which may indicate poor dilation in the lesion area, and high collateral function, which may divert blood from the lesion. Other factors influence eNOS, which synthesizes the vasodilator NO. These are an eNOS SNP associated with restenosis, which may decrease eNOS function, and asymmetric dimethyl arginine, which inhibits eNOS and which is increased in the blood of restenotic patients.[84] Finally, a beta2 adrenergic receptor SNP may decrease the vasodilatory function of this receptor[30] (Table 7.1).

Origin of intimal cells

Early experiments on the arterial response to injury indicated that medial SMCs were the source of intimal cells after injury (see [2]), but more recent studies of arterial injury in chimeric mice and rats suggested that a significant number of intimal SMCs are of bone marrow origin(review in;[154,155] see

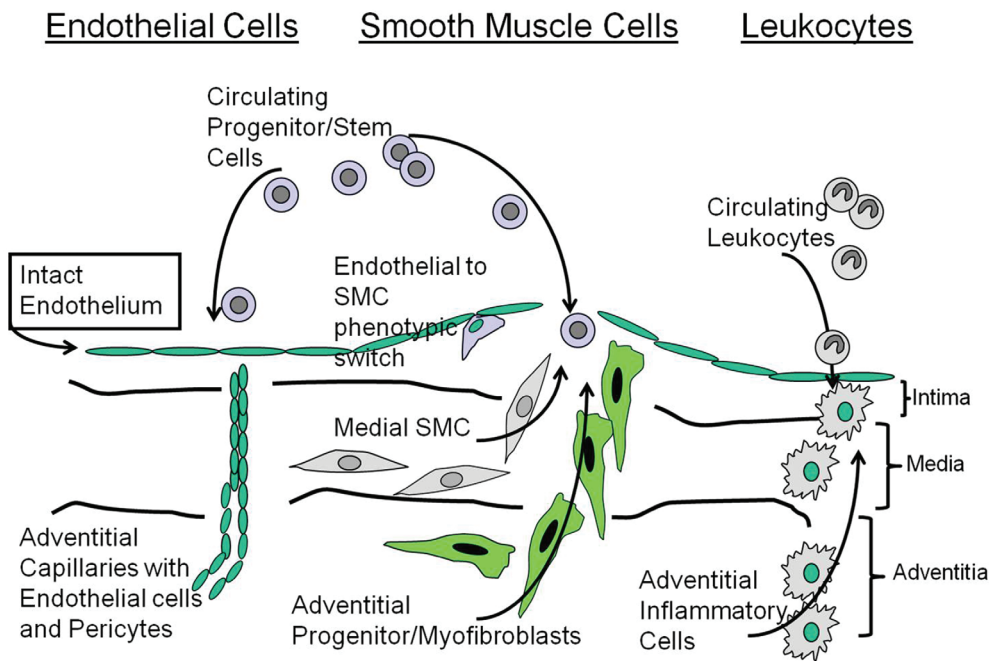

FIGURE 7.2: Possible sources of intimal cells after arterial injury.

figure 7.2 for possible sources of the major cells of the intima). However, these data have been called into question by investigators using more robust microscopic techniques for detecting double labeled cells.[156-159] In addition, while some studies have shown a correlation between the risk of human coronary BMS restenosis and the increase in circulating $CD34^+$ cells and their ability to differentiate into SMCs in vitro,[78,80] the significance of these data is not clear in the absence of data showing a contribution of these cells to intima formation in humans. Another possible source of intimal cells is suggested by studies in rats, pigs, and rabbits that indicate that adventitial cells migrate into the intima (review in[160]). However, other investigators did not find significant adventitial involvement in porcine coronary intima formation with[161,162] or without complete interruption of the media (see review[154]). While recent reports demonstrate the presence of adventitial cells in rat and human arteries and veins that can differentiate into SMCs, the contribution of adventitial cells to intimal hyperplasia remains uncertain.[158,163,164] In addition, evidence from studies of embryonic development and with cultured endothelial cells demonstrate that endothelial cells can undergo a phenotypic transition to SMCs making these another potential source of intimal cells.[165] Overall, the data suggest a medial and possibly adventitial origin of intimal SMCs.

Inflammation

There is a strong correlation between inflammation and restenosis after angioplasty or stent placement[15,166] and between macrophages in the primary lesion and the occurrence of restenosis after angioplasty[167] (reviewed in[168]). While many individual studies have not demonstrated an independent association between pre-procedural blood levels of the acute phase protein, CRP, and coronary restenosis, a meta-analysis of

coronary angioplasty studies showed CRP as an independent predictor (Table 7.1). In addition, a study of peripheral angioplasty showed a much stronger relationship between restenosis and 48 hour post-angioplasty CRP levels than with pre-procedural levels.[58] Whether CRP is related to vein graft stenosis is not clear.[169]

Data from models of injury that both do and do not denude the vessel of endothelium indicate that inflammation promotes intimal hyperplasia. Leukocyte recruitment to the injured vascular wall occurs via binding to adherent platelets[170] and to cell adhesion molecules that are up-regulated by injury, such as ICAM-1 and VCAM-1.[171] Knockout or blockade of VCAM-1 or of the inflammatory cell integrin, Mac1, inhibits lesion formation after injury because of decreased leukocyte recruitment.[10,172,173] Inhibition of monocyte recruitment using a dominant-negative mutant of MCP-1, a major monocyte chemoattractant, also inhibits intimal hyperplasia after angioplasty in rats, non-human primates,[174] and hypercholesterolemic rabbits.[175] Finally, simultaneous myocardial infarction increases intimal hyperplasia after femoral artery injury possibly via increased levels of circulating IL-6 and TNFα.[176]

A number of inflammatory factors are predictors of restenosis. The number of inflammatory cells in stented lesions,[15] activation status of Mac1 on leukocytes,[73] a CD18 (a Mac1 subunit) SNP,[74] and the change in blood levels of MCP-1 are associated with restenosis[75,177] (Table 7.1). Of note, rapamycin is anti-inflammatory.[178] In addition, prednisone, another anti-inflammatory drug, decreases late lumen loss in coronary BMS and the release of TNFα from the patients' monocytes. This reduction in TNFα release correlates with late lumen loss[179] (Table 7.1). However, there are conflicting results with the -174 G/C and -511 polymorphisms of IL-6 and IL-1, respectively, in studies of the coronary and peripheral circulation.[66,69,180] Despite this there is a clear association of inflammation with restenosis.

Role of ECM production

Both cell proliferation and ECM production contribute to intimal hyperplasia[131], and intimal area more than doubles between two and eight weeks after injury because of ECM accumulation. The stable neointima is about 20% SMCs and about 80% ECM.[131] Rates of SMC replication are extremely low in restenotic tissue,[5,181] leading Glover and colleagues to suggest that changes in ECM are the major factor in restenosis several months to years after stent placement. Of interest, re-injury to the rat carotid artery one month after a prior balloon injury increases intimal lesion size entirely as a result of increased ECM.[182] In this regard, it should be noted that rapamycin inhibits induction of major ECM proteins such as collagen and hyaluronan.[183,184] The lack of evidence for substantial SMC proliferation in either angioplasty or stent stenosis suggests that therapies may be better aimed at altering the synthetic phenotype of SMCs, which would control ECM synthesis as well as proliferative capacity.

THE CONTRIBUTION OF SPECIFIC FACTORS TO RESTENOSIS

Growth factors/cytokines

Activated platelets, leukocytes, endothelial cells, macrophages, and SMCs can release a great number of growth factors and cytokines after arterial injury, including PDGF, FGF2, TGFβ, TGFα, vascular endothelial cell growth factor, macrophage colony stimulating factor, granulocyte macrophage colony stimulating factor, platelet-derived endothelial cell growth factor, IL-1, IL-4, IL-6, IL-8, IL-18, MCP, and TNF.[185] Many

of these factors have been shown to play roles in intimal hyperplasia and remodelling after arterial injury,[2] but we will focus on only three of these factors.

PDGF is a family of four gene products (A, B, C, and D chains) that dimerize into five functional growth factors (AA, AB, BB, CC, and DD), which bind differentially to homo- or hetero-dimers of two receptor subunits, α and β (see review[186]). PDGF plays a major role in the migration of SMCs after injury, while playing a minor role in SMC proliferation.[186] The β receptor subunit mediates intimal hyperplasia in non-human primates, which suggests a role for the PDGF isoforms B and D, and possibly C. However, there is also evidence for a role of PDGF-AA and, therefore, PDGF receptor α in intimal hyperplasia in the rat.[186] Of interest, concomitant treatment of non-human primates with blocking antibodies to both PDGF receptor isoforms causes intimal regression in polytetrafluroethylene grafts, while treatment with either alone does not.[187] A single intravenous infusion of a humanized version of this PDGFRβ antibody did not alter BMS restenosis,[188] but plasma concentrations considered effective were maintained for only two weeks.

FGF2 stimulates medial SMC proliferation and migration to the intima in the injured rat carotid, and blockade of both FGF2 and PDGF with antibodies results in an additive inhibition of intimal hyperplasia. However, FGF2 plays no role in the proliferation of intimal SMCs, and the intimal hyperplastic response in FGF2 knockout mice is normal (see review[2]). However, these mice display decreased SMC contractility,[189] which is consistent with the observation that a blocking antibody to FGF2 inhibits negative remodelling in the mouse carotid tie-off model.[190]

Although infusion of TGFβ1 stimulates medial SMC proliferation and antibody blockade slightly inhibits intimal hyperplasia, the more striking effect of blocking the action of TGFβ is on remodelling and ECM production (see review[191]). Blockade of TGFβ with a soluble receptor blocks negative remodelling, the transition of adventitial fibroblasts to myofibroblasts, and the deposition of collagen and versican. In stents, blockade of the TGF receptor does not alter intimal thickening but alters inflammatory cell number and extracellular matrix composition.[192]

Interactions among growth factors after injury are a significant though largely unexplored aspect of restenosis. For example, TGFβ can synergistically augment the mitogenic action of PDGF and FGF2.[191] In addition, IL-1β augments the proliferative effect of PDGF-BB on SMCs by inhibiting expression of p21 and p27, but inhibits PDGF-BB mediated SMC migration (see review[2]). Such interactions may augment hyperplasia in areas of inflammation (such as near stent struts) by slowing SMC movement and increasing proliferation.

Inhibitors

Numerous factors are inhibitors of intimal hyperplasia. For example, NO can inhibit SMC migration and proliferation after arterial injury[149] and prostacyclin inhibits intimal hyperplasia via its receptor IP.[193] Heparin and the heparan sulfate proteoglycans, perlecan and syndecan-1, inhibit SMC proliferation and migration, thus inhibiting injury mediated intimal hyperplasia.[194-196] In addition, overexpression of heparanase, the enzyme responsible for degrading the heparan sulfate glycosaminoglycans, causes increased intimal hyperplasia after stent-induced injury.[197] The normal adventitia inhibits medial SMC migration and proliferation.[121] Similarly, normal periadventitial adipose tissue inhibits intimal hyperplasia after injury at least partially through the action of adiponectin.[198] Other factors known to inhibit intimal hyperplasia

include interferon γ, hepatocyte growth factor, interleukin 10, adrenomedulin, somatostatin, and endothelin.[2]

In recent years, it has become clear that the effect of a single ligand is often dictated by the relative expression of receptor isotypes, which can have opposing roles. For example, in the vascular system S1P binds to the GPCRs, S1PR1, 2, and 3. Data indicate that S1PR1 and S1PR3 are stimulators of intimal hyperplasia after injury, while S1PR2 is an inhibitor in this regard.[199] Another GPCR ligand, LPA, binds to LPA1 through 5. LPA1 is inhibitory towards SMC migration, while LPA3 appears to be stimulatory.[200] Prostaglandin E_2 also binds to GPCRs, EP1 through EP4. Receptors EP_1 and EP_3 induce vasoconstriction, whereas EP_2 and EP_4 induce vasodilatation.[201] Activation of EP4 increases ductus intimal cushion formation[202] suggesting the possibility that other EP receptors may mediate the growth inhibitory effects often described for PGE in vitro.

Coagulation and fibrinolytic factors

Arterial injury in pigs and primates is associated with thrombosis, which is usually not occlusive but does release mediators of SMC growth and migration. Rodent models of arterial injury are usually not associated with thrombus formation,[203] although it is possible that intimal hyperplasia is being driven by short-lived microthrombi or by thrombogenic factors such as TF[7], thrombin,[204] and factor Xa[205] at levels too low to generate thrombus formation. While TF drives intimal hyperplasia after injury because of increased SMC migration[7], after double injury TF mediates negative remodelling,[206]

Balloon injury also increases expression of the plasminogen activators, urokinase and tissue-type plasminogen activator, in SMCs (review [207]). The plasminogen activators, in turn, proteolytically activate plasmin, which has a major role in fibrinolysis. Several lines of evidence indicate that urokinase is also required for SMC migration and proliferation.[207,208] In this regard plasma urokinase is a predictor of restenosis.[87] Also of interest, the urokinase receptor interacts with PDGF receptor β which in turn mediates the effects of urokinase on migration and proliferation in a PDGF-independent manner.[209] Finally, in contrast to urokinase, tissue plasminogen activator has been shown to inhibit SMC accumulation after injury and to cause positive arterial remodelling.[207]

Matrix metalloproteinases

MMPs are involved in the regulation of both intimal hyperplasia and remodelling. Arterial injury in numerous species induces the production of a number of MMPs, including MMPs 2, 3, and 9,[208,210] which promote intimal hyperplasia and are associated with BMS restenosis (Table 7.1).[89-92] For example, MMP9 is increased in coronary sinus blood after stent placement and is associated with increased levels of $CD34^+$ progenitor cells,[211] which are predictors of restenosis (Table 7.1). High blood flow-mediated positive remodelling is mediated by MMP9.[212-213] Blockade of MMPs with synthetic drugs has mixed results on intimal hyperplasia and remodelling[2] probably because of the lack of specificity of small molecule inhibitors. In addition, hydroximate-based MMP inhibitors can inhibit MAP kinase signaling and collagen synthesis, which itself can inhibit SMC migration.[2] Finally, there are active site independent effects of MMPs as demonstrated by the inhibitory effect of MMP9 on SMC-mediated collagen gel contraction.[214]

Extracellular matrix/receptors

At late times after arterial injury as SMC proliferation decreases, intimal hyperplasia

continues as the result of ECM accumulation. Restenotic tissue from humans demonstrates lower cell density and substantial amounts of an ECM that differs from primary atherosclerotic lesions from which restenotic lesions arise.[5,215] ECM molecules induced by angioplasty[216] and stenting[217] include type I collagen, elastin, and hyaluronan as well as the proteoglycans versican, perlecan, biglycan, and decorin. The ECM of restenotic lesions has more biglycan and hyaluronan[181,216,218,219] and no decorin, unlike primary plaques.[5] Consistent with lesion formation during restenosis, both biglycan and hyaluronan increase SMC proliferation, while decorin inhibits ECM accumulation after injury.[220-222]

Cellular receptors for ECM components by which SMCs might act to remodel the artery includes the integrins, discoidin domain receptors, TLRs, and CD44, all of which are induced after vascular injury.[223-226] The family of integrins provides the classic example of a binding partner, which is able to mediate subcellular signaling.[227] Blockade of $\alpha v\beta 3$ integrin inhibits intimal hyperplasia without an effect on arterial remodelling.[228] The stimulatory effect of CCN1, an ECM protein upregulated by injury, on intimal hyperplasia may be via interaction with integrins.[229] Discoidin domain receptor 1, first described as a signaling receptor of collagens, is required for SMC migration and MMP production.[230] CD44 binds hyaluronan, collagens, and other ECM molecules and mediates SMC proliferation, migration, and SMC-mediated collagen gel contraction.[231,232] TRL2 and TLR4, which are important components of the innate immune system, recognize not only microbial components but also endogenous molecules such as versican, biglycan, heparan sulfate, and hyaluronan.[233-235] Both TLR2 and TLR4 appear to be required for cuff-mediated intimal hyperplasia[226,236] and TLR4 is also required for high blood flow-mediated outward remodelling.[237] MyD88, which is a major intracellular mediator of TLR signaling, is also required for flow-mediated remodelling.[238]

TARGETS FOR INTERVENTION

Intracellular signaling molecules

mTOR and microtubules

Current interventions that significantly prevent restenosis utilize DES for the local application of either rapamycin or taxol related drugs.[6] The molecular targets of rapamycin and taxol are mTOR and microtubules, respectively (see review[239]). Rapamycin is known to function as an antiproliferative drug through the inhibitory effect of a rapamycin/FKBP12/mTOR complex. This complex inhibits pro-proliferative molecules such as $p70^{s6k}$ and inhibits anti-proliferative molecules such as p27.[239] mTOR has two isoforms, mTORc1 and mTORc2. Inhibition of the latter isoform appears to mediate endothelial cell toxicity that can lead to thrombosis.[240] Newer rapamycin analogs, such as everolimus and zotolorimus, show promise of decreasing problems with late thrombosis.[6] The other primary type of drug currently used in DES is paclitaxel, which binds to the β subunit of tubulin thereby stabilizing microtubules and preventing mitotic spindle formation during cell division. However, this drug also has cell-cycle independent effects on cell spreading and migration.[239]

Transcription factors

One transcription factor that has been targeted is E2F, a family of transcription factors required for DNA synthesis and cell cycle progression. Two large clinical trials of an inhibitor of E2F were based on animal studies in which an E2F decoy (a short

double-stranded oligodeoxynucleotide that binds E2F) blocked intimal hyperplasia. Saphenous vein grafts were treated with the E2F decoy before implantation for coronary (PREVENT IV) or peripheral (PREVENT III) bypass. However, neither trial of 3400 and 1600 patients, respectively, showed an effect on graft failure.[241,242] Unfortunately, the use of a non-selective E2F decoy that inhibits all E2F family members may have cancelled out an effect, since a more recent study indicates that E2F3 stimulates and other E2F family members inhibit SMC proliferation and intimal hyperplasia.[243] Despite these negative results vein grafts still provide an exceptional opportunity for intervention ex vivo before implantation. In preclinical studies, other transcription factor targets using the decoy technology have included Egr-1, which has been implicated in many cardiovascular disorders.[244]

miRNA

It is likely that future targets will include miRNAs, since these small RNA molecules regulate multiple gene products and it is unlikely that a single gene will regulate all pathways of a complex pathology like restenosis. Possible miRNA targets include Mir-21, Mir26a, Mir143/145, and MiR-221, which have been shown to regulate SMC phenotype, growth, death, and migration as well as intimal hyperplasia.[245-248]

Inflammation targets

One anti-inflammatory drug that has been tested is pimecrolimus. This drug binds to the cytosolic receptor FK506 binding protein, which inhibits the calcium-dependent phosphatase calcineurin and the translocation of the transcription factor, nuclear factor of activated T-cells, to the nucleus preventing induction of inflammatory cytokines in T cells and mast cells. Based on animal models this was expected to reduce arterial inflammation and, therefore, neointimal hyperplasia and restenosis.[249] Instead, patients treated with pimecrolimus-eluting stents were reported to fare worse than patients treated with stents that delivered a combination of pimecrolimus and paclitaxel, or paclitaxel alone.[250] However, other drugs are being tested. An anti-inflammatory drug with a long history, salicylic acid, is being tested as a component of the biodegradable backbone of a stent that also has a coat of sirolimus.[251] Finally, liposomal alendronate, a bisphosphanate compound that depletes monocytes and inhibits restenosis in rat and rabbit models of injury, is in phase II trials testing its effects on BMS restenosis (http://clinicaltrials.gov/ct2/show/NCT00739466). Overall it appears that targeting inflammation alone may be inadequate to inhibit restenosis, although it may be effective as an adjunctive target.[249]

Brachytherapy

Brachytherapy (radiation treatment) has shown success as an adjunctive therapy for BMS restenosis after successful balloon angioplasty.[6] While brachytherapy inhibits both negative remodelling and intimal hyperplasia, one limitation found initially was hyperplasia at the ends of the stents or the angioplasty zone when radiation was not complete.[5,252] In addition, prior brachytherapy is a risk factor for stent thrombosis.[6] Brachytherapy is less common now because of procedural logistics, concern of long-term thrombosis and delayed restenosis, but more importantly the availability of DES.[6]

Extracellular targets and cell-based therapies

Angiotensin pathway

While angiotensin II type 1 receptors mediate vascular SMC migration, proliferation, and extracellular matrix production after arterial

injury and angiotensin-converting enzyme inhibitors or specific receptor antagonists reduced intimal hyperplasia in several animal models, large scale trials of the angiotensin-converting enzyme inhibitor, cilazapril, for balloon angioplasty or BMS failed to show benefit.[120] However, more recent studies show that neointimal hyperplasia is inhibited by the angiotensin-converting enzyme inhibitor, quinapril, in patients with the D/D and I/D genotypes of angiotensin-converting enzyme.[253,254] In addition, use of the angiotensin II type 1 receptor antagonist, valsartin, decreases the incidence of stent restenosis[255] and a valsartin-eluting stent is equivalent to a rapamycin-eluting stent.[256] These data suggest that angiotensin II type 1 receptor antagonists may be useful in preventing restenosis.

Cell-based therapies

Use of engineered allogeneic endothelial cells applied to the adventitial surface to prevent restenosis in peripheral interventions is in Phase I/II trials at this time (http://clinicaltrials.gov/ct2/show/NCT01099215). This trial is based on work in a porcine stent model[257] and utilizes the same concept as a trial aimed at inhibiting stenosis of arterio-venous fistula bypass grafts.[258] A Phase IV study involving endothelial cells utilizes a coronary stent with immobilised anti-CD34 antibody with which to capture circulating endothelial progenitor cells (http://clinicaltrials.gov/ct2/show/NCT00494247).[259] Finally, the possibility of bioengineered bypass grafts developed from induced pluripotent stem cells or other autologous progenitors holds promise as these may also be engineered to express or repress targets of choice.[260]

Differential effects on endothelium and SMCs

A differential effect on endothelium compared to SMCs is a helpful attribute for any target for restenosis. The lack of selectivity is a problem for rapamycin for which effects on endothelium mediate its thrombotic side effects. A20 is a zinc finger protein that prevents intimal hyperplasia in the injured rat carotid artery[261]. Expression of A20 in medial SMCs prevents neointima formation by shutting down inflammation and proliferation via inhibition of NF-κB and by increased expression of the cell cycle dependent kinase inhibitors $p21^{waf1}$ and $p27^{kip1}$. However, A20 is anti-inflammatory in endothelial cells by inhibiting NFκB, but this is antiapoptotic via inhibition of the activation of caspase 8. Therefore, A20 has protective effects for endothelial cells and anti-proliferative effects on SMCs making it a good candidate for inhibiting SMC accumulation while minimizing endothelial damage. Another differentially effective target may be Nogo. Nogo-B is expressed by both endothelial cells and SMCs, but it increases endothelial cell migration and inhibits SMC migration. Nogo-B is down-regulated after injury and intimal hyperplasia is greatly increased in the Nogo-B null mouse. Transfection of the murine arterial adventitia or porcine vein graft adventitia with an adenoviral vector of Nogo-B greatly inhibited intimal hyperplasia.[262]

Delivery devices

Garg et al have recently reviewed the use of DES and future design technology for the coronary arteries.[6,251] The issue of drug-eluting polymers is an area of advancement with next generation polymers, including biodegradable polymers, avoiding many of the past problems with allergic and inflammatory reactions. In addition, biodegradable stents with and without anti-proliferative drugs are under development. These would avoid long term issues of inflammation from a foreign body. Stents with multiple therapeutic targets are under

development. One example is a DES that targets SMC proliferation and platelets with sirolimus and cilostazol, respectively. Bi-directional drug delivery from stents may allow functional separation of effects on SMCs and endothelial cells. Finally, as more is learned about the effects of co-morbitities on restenosis, such as diabetes, specific DES or drug-eluting balloons may be developed to use in subsets of patients.

A common treatment of in-stent restenosis is the use of DES. However, it is unclear if another stent adds to the risk of stent thrombosis or reoccurrence of restenosis. Drug-eluting balloons are being studied as an alternative for this situation. In addition, DES have not shown benefit in femoropopliteal arteries, which are often significantly occluded throughout their length and are subject to forces not experienced by coronary arteries (e.g. compression and bending) that may cause strut fracture.[263] Drug-eluting balloons have shown promise on peripheral artery lesions.[264] One advantage of drug-eluting balloons is illustrated by a study of the use of nanoparticles, since the nanoparticles move further into the vascular wall before eluting their drug cargo and thus avoid endothelial cell toxicity.[125] There are many differences between DES and drug-eluting balloons including the issue of drug delivery kinetics. These as well as current and past trials with drug-eluting balloons are reviewed by Gray.[265]

Prevention vs. reversal of restenosis

Because current strategies to treat restenosis are intended to prevent intimal hyperplasia, all patients must be treated, even though less than one-third of all vascular interventions fail. Other options are to develop the ability to screen for those patients at high risk or to develop a treatment that would reverse the restenotic process.[261] Observations of various SNPs and soluble factors associated with restenosis (Table 7.1) suggest that screening may be possible in the future. The possibility of reversing the restenotic process comes from the observation that intima formation in stents increases for about 3 months, but starts regressing spontaneously after 6 months[261], as well as effects of anti-hypertensive drugs and of A20, which induce vascular regression via SMC apoptosis.[261,266] In addition, when global gene expression is compared in two distinct models of vascular regression in non-human primates, only 7 genes are regulated in the same manner in *both* models of atrophy (Kenagy et al, in press). Six of these atrophy-associated genes are also induced in vitro by the ligand for the death receptor Fas, suggesting that these genes are an important part of the cell death program active during atrophy. Also, a third of the up-regulated genes (ADAMTS4, tissue plasminogen activator, and hyaluronidase2) degrade components of the ECM, loss of which is a major feature of vascular atrophy. These commonly regulated genes may play a fundamental role in vascular atrophy and may lead to drug candidates useful for reversing restenosis in those situations where intimal hyperplasia is the primary cause.

CONCLUSIONS

Restenosis is primarily a problem of excessive intimal hyperplasia and negative remodelling. Human risk factors for restenosis include diabetes, renal failure, factors associated with decreased blood flow, factors leading to decreased growth inhibition, factors leading to increased growth stimulation, as well as increased inflammation (Table 7.1). These data are consistent with data from animal models of intimal hyperplasia and support further research into how these factors impact restenosis. While animal models have been useful for understanding basic mechanisms

of restenosis, the predictive power of animal models for clinical efficacy is still unclear, particularly concerning peripheral vessels. Correlating animal models and clinical application is an active area of research.[267] In addition, most clinical studies are of the coronary circulation. The degree to which results in the coronary circulation match the peripheral circulation is not known, but there are differences. Coronary and peripheral vessels are embryologically distinct,[268] and injury of the coronary artery leads to greater intima formation than does injury of peripheral arteries in pigs and dogs.[269-271] In addition, the femoropopliteal arteries, but not the coronary arteries, are subject to the forces of compression, bending, twisting, and axial changes caused by joint flexion and external impact, which may have a significant effect on restenosis.

Our greatest success at preventing restenosis, DES, comes as much as a result of engineering than of drug development. As endovascular techniques continue to evolve, the efficacy of drug targets should keep pace. Unfortunately, the early promise of the Human Genome Project for new therapeutics aimed at human disease such as restenosis has not been forthcoming. Genome-wide association studies, designed to reveal markers or potential causal factors, have revealed that cardiovascular pathologies have a complex genetic structure. While >20,000 genes and more regulatory factors of the RNA world have been identified, how these factors are related remains largely unknown. However, the field of systems biology is poised to have a significant impact on vascular biology over the coming decade. New types of analysis have revealed networks that can explain up to 50% of the variance of a complex clinical phenotype.[272-273] It is hoped that a systems biology or similar approach will soon reveal key networks and regulatory hub molecules that control restenosis. Based on research to date it is likely that networks regulating cell differentiation, growth, inflammation, and ECM production, major aspects of intimal hyperplasia, will be featured and that hub molecules that link these networks will be identified as promising therapeutic targets.

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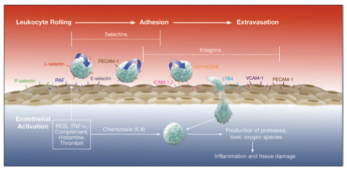

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Mechanisms of Vascular Disease

Edited by Robert Fitridge and Matthew Thompson

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