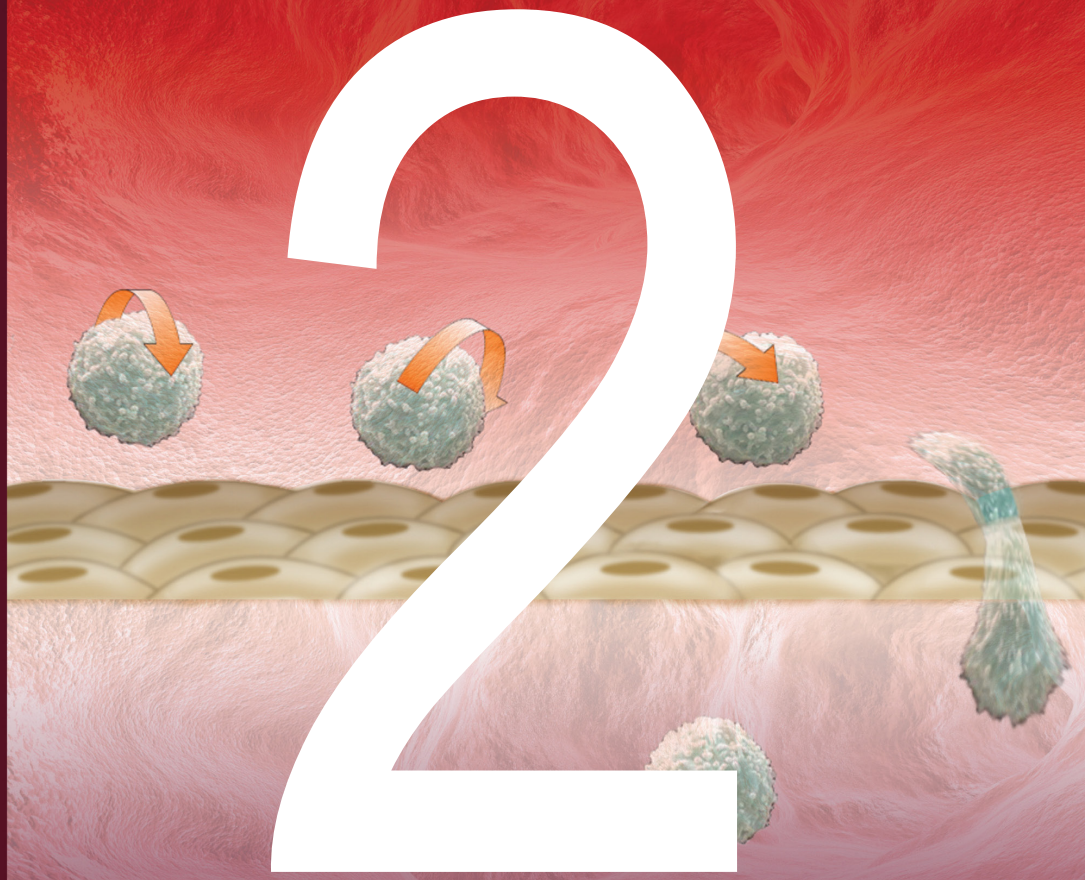
Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists



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A Reference Book for Vascular Specialists

Robert Fitridge
The University of Adelaide, The Queen Elizabeth Hospital, Woodville, Australia
Matthew Thompson
St George's Hospital Medical School, London, UK

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List of Contributors

David G Armstrong
The University of Arizona
Southern Arizona Limb Salvage Alliance
Tucson, AZ
USA

Vishwanath Biradar
Intensive Care Unit
The Queen Elizabeth Hospital
Woodville, SA
Australia

Matthew Bown
Department of Vascular Surgery
University of Leicester
Leicester
UK

Andrew W Bradbury
University Department of Vascular Surgery
Birmingham Heartlands Hospital
Birmingham
UK

Edward Choke
Department of Vascular Surgery
University of Leicester
Leicester
UK

Gillian Cockerill
Department of Clinical Sciences
St George's Hospital Medical School
London
UK

Prue Cowled
Department of Surgery
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Helen Daly
Royal Perth Hospital
Perth, WA
Australia

Mital Desai
University Department of Vascular Surgery
Royal Free Hospital
University College
London
UK

Robert F Diegelmann
Department of Biochemistry
Medical College of Virginia
Richmond, VA
USA

Timothy K Fisher
Rashid Centre for Diabetes and Research
Sheikh Khalifa Hospital
Ajmon
UAE

Robert A Fitridge
Department of Surgery
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Gail Gillespie
Royal Perth Hospital
Perth, WA
Australia

Jonathan Golledge
Vascular Biology Unit
School of Medicine & Dentistry
James Cook University
Townsville, QLD
Australia

George Hamilton
University Department of Vascular Surgery
Royal Free Hospital
University College
London
UK

Mark Hamilton
Department of Surgery
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Robert J Hinchliffe
St George's Vascular Institiute
St George's Hospital
London
UK

Richard D Kenagy
Department of Surgery
University of Washington
Seattle, WA
USA

Paul Kerr
Department of Pharmacology
University of Alberta
Alberta
Canada

Michael MD Lawrence-Brown
Curtin Health Innovation Research Institute
Curtin University
Perth, WA
Australia

Brian Lepow
The University of Arizona
Department of Surgery
Southern Arizona Limb Salvage Alliance
Tucson, AZ
USA

Kurt Liffman
CSIRO Material Science & Engineering and School of Mathematical Sciences
Monash University
Melbourne, Vic
Australia

Ian Loftus
Department of Vascular Surgery
St George's Hospital
London
UK

Mark J McCarthy
Department of Surgery and Cardiovascular Sciences
University of Leicester
Leicester
UK

Greg S McMahon
Department of Surgery and Cardiovascular Sciences
University of Leicester
Leicester
UK

Simon McRae
Adult Haemophilia Treatment Centre
SA Pathology
Adelaide, SA
Australia

Joseph L Mills
The University of Arizona
Southern Arizona Limb Salvage Alliance
Tucson, AZ
USA

Lyle Moldawer
Department of Surgery
University of Florida
Gainesville, FL
USA

John L Moran
Faculty of Health Sciences
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Stephen Nicholls
The Heart and Vascular Institute
Cleveland Clinic
Cleveland, OH
USA

Ian M Nordon
St George's Vascular Institiute
St George's Hospital
London
UK

Paul E Norman
School of Surgery
University of WA
Fremantle, WA
Australia

Karlheinz Peter
Baker IDI Heart & Diabetes Institute
Melbourne, Vic
Australia

Frances Plane
Department of Pharmacology
University of Alberta
Alberta
Canada

Janet T Powell
Imperial College
London
UK

Sandeep Prabhu
Baker IDI Heart & Diabetes Institute
Alfred Hospital
Melbourne, Vic
Australia

Rishi Puri
The Heart and Vascular Institute
Cleveland Clinic
Cleveland, OH
USA

Stephan A Schug
Royal Perth Hospital
Perth, WA
Australia

Gregory S Schultz
Department of Obstetrics and Gynaecology
University of Florida
Gainesville, FL
USA

Rahul Sharma
Baker IDI Heart & Diabetes Institute
Alfred Hospital
Melbourne, Vic
Australia

Guo-Ping Shi
Department of Cardiovascular Medicine
Brigham & Women's Hospital
Harvard Medical School
Boston, MA
USA

Michael Stacey
University Department of Surgery
Fremantle Hospital
Fremantle, WA
Australia

Ilija D Sutalo
CSIRO Material Science & Engineering
and Curtin Health Innovation
Research Instutute
Curtin University
Highett, Vic

Raymond Tam
Department of Pharmacology
University of Alberta
Alberta
Canada

Matthew Thompson
St Georges Hospital Medical School
London
UK

Martin Veller
Department of Surgery
University of Witwatersrand
Johannesburg
South Africa

Mauro Vicaretti
Department of Vascular Surgery
Westmead Hospital
Westmead, NSW
Australia

Matt Waltham
Academic Department of Surgery
St Thomas' Hospital
London
UK

Matthew L White
Vascular and Endovascular Surgery
University of Arizona
Tucson, AZ
USA

David P Wilson
School of Medical Sciences
Discipline of Physiology
University of Adelaide
Adelaide SA
Australia

Qingbo Xu
Department of Cardiology
Kings College
University of London
UK

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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

2 • Vascular Smooth Muscle Structure and Function

DAVID P WILSON

Molecular Physiology of Vascular Function Research Group,
Discipline of Physiology, University of Adelaide, South Australia

INTRODUCTION

Smooth muscle has an important role in regulating the function of a variety of hollow organ systems including the: vasculature, airways, gastrointestinal tract, uterus and reproductive tract, bladder and urethra and several other systems. Smooth muscle has two fundamental roles: 1) to alter the shape of an organ and 2) to withstand the force of an internal load presented to that organ. In order to achieve these fundamental objectives smooth muscles have developed mechanisms of mechanical coupling, which enable the development of powerful and coordinated contractions at a relatively low energy cost. For example, smooth muscle in the gastrointestinal tract must undergo intermittent but coordinated phasic contractions to propel the bolus of food through the alimentary canal. Whereas in the airways and vasculature the smooth muscle is more often in various states of tonic contraction, but can be dynamically regulated to relax or contract in response to specific neuro-hormonal and haemodynamic signals. In keeping with the aims of this text, this chapter will focus on the principle mechanisms through which vascular smooth muscle functions.

SMOOTH MUSCLE (VASCULAR) STRUCTURE

Vascular smooth muscle cells have classically been envisaged as fusiform cells, on average 200 microns long × 5 microns in diameter, with a large central nucleus surrounded by an abundant array of endoplasmic reticulum and golgi apparatus, with the cytosol and plasma membrane tapering toward the poles. Although the dimensions of the vascular smooth muscle cell narrow toward their ends there is clear evidence that the end-to-end junctions coupling smooth muscle cells are complex and contain a significant number of membrane invaginations to provide increased surface area for both mechanical tight junctions and electrical coupling via gap junctions (Figure 2.1). Vascular smooth muscle cells do not contain the complex t-tubule/sarcoplasmic reticulum system common to striated muscles, but rather they contain a significant number of invaginations along the plasma membrane called caveolae, which serve a similar, albeit less developed role to increase the cellular surface: volume ratio. These specialized caveolae further provide a unique plasma membrane environment, which enables clustering of specific groups

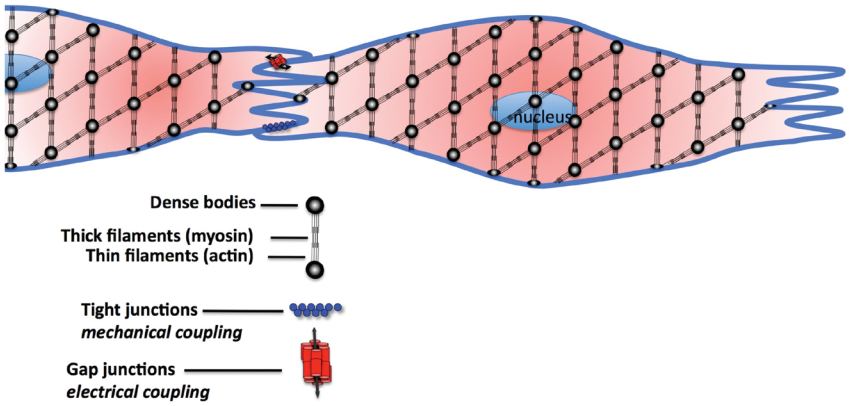

FIGURE 2.1: Highlights the fusiform shape of typical smooth muscle cells and the patterned array of actin myosin myofilaments across the cell. Smooth muscle cells have invaginations along their length to provide increased surface area for mechanical coupling via tight junctions and electrical coupling through Gap junctions. Dense bodies are thought to be similar to Z-disks found in striated muscle.

of ion channels and receptors important in cellular signal transduction.

In contractile vascular smooth muscle the endoplasmic reticulum has been modified to enable Ca^{2+} release and reuptake and has therefore been termed sarcoplasmic reticulum. In smooth muscle cells the sarcoplasmic reticulum/endoplasmic reticulum (SR/ER) complex comprises about 5% of the total cell volume, with a considerable amount of rough endoplasmic reticulum and golgi apparatus adjacent to the nucleus, which reflects the significant capacity that smooth muscle has for protein synthesis and secretion. The fact that vascular smooth muscle has a fundamental role in mediating pressure and flow in the vasculature is reflected in the abundance of cytoskeletal and contractile proteins expressed.

CYTOSKELETON

As with all eukaryotic cells the cytoskeleton is comprised of a network of many and various filamentous proteins, often formed by the polymerization of monomeric subunits. For example, monomers of alpha and beta tubulin self assemble into microtubules that function to provide static support to the cell and to enable motor protein mediated transport of cytosolic cargo and for chromosomal segregation during mitosis. The actin cytoskeleton and elements of the actin contractile myofilament are also generated from the polymerization of globular monomeric actin to form polymeric actin filaments. This process is dynamically regulated even within the time scale of contractile processes, i.e., as the smooth muscle slowly shortens it can actually synthesise and extend the length of the actin filaments.

CONTRACTILE MYOFILAMENT

The structure of the smooth muscle acto-myosin array is similar to striated muscle with several important differences:

1. there is no troponin complex in smooth muscle
2. contraction is regulated by Ca^{2+} calmodulin-dependent myosin light chain kinase (MLCK) mediated phosphorylation of the regulatory light chains of myosin, which enables actin

myosin interaction and cross bridge cycling
3. in the absence of Ca^{2+} and calmodulin (CaM), caldesmon interacts with actomyosin inhibiting the activity of myosin ATPase
4. the activity of myosin light chain phosphatase (MLCP) directly causes the dephosphorylation of myosin LC_{20} leading to relaxation
5. the actin: myosin ratio is higher in smooth muscle averaging 15:1 in vascular smooth muscle in comparison to 6:1 in skeletal or cardiac muscle. There are no intercalated disks or z-disks, however, dense bodies in smooth muscle are thought to be analogous to z-disks (Figure 2.2).

There are a variety of intermediate filament proteins but desmin and vimentin are particularly abundant in smooth muscle. In fact, desmin has been shown to be upregulated in several myopathies and during smooth muscle hypertrophy. As indicated once globular actin polymerizes into filaments they coil to form mature filamentous actin that then combines with tropomyosin to form a large actin-tropomyosin filament which together is arranged in side polar arrays with myosin II filaments (Figure 2.1). The myosin II thick filaments are composed of two 200kDa heavy chains, two 17kDa light chains and two phosphorylatable regulatory myosin light chains (LC_{20}). The two heavy chains coil together forming a 155nm rod, while the globular head contains the motor domain consisting of light chains and Mg^{2+} ATPase activity and the actin binding domain. The myosin is arranged in an anti parallel array that enables the myosin motors, on the heads of myosin molecules, to draw actin polymers along its length and effect shortening of the cell, so-called cross bridge cycling (Figure 2.2). MLCK, which is responsible for the Ca^{2+} calmodulin mediated phosphorylation of LC_{20} is actin associated while MLCP which removes the phosphoryl groups from LC_{20} is associated with myosin. (Figure 2.3)

FUNCTIONAL REGULATION OF VASCULAR SMOOTH MUSCLE: NEURONAL, HORMONAL, RECEPTOR MEDIATED

Smooth muscle from all hollow organs including blood vessels have been somewhat artificially categorized into either single unit smooth muscle or multiunit smooth muscle, when in reality they should likely be considered as a combination of both types. Nevertheless, historically, multiunit smooth muscle has been considered to be regulated primarily through autonomic sympathetic innervations, which release neurotransmitters from varicosities along the axon, rather than specifically coupling to individual cells. Consequently, neurotransmitters are required to diffuse anywhere from 5-100 nm to the adjacent smooth muscle membrane in order to activate their receptors. The activation of sympathetic nerves therefore causes membrane depolarization and activation of voltage dependent ion channels, the most prominent of which are the clinically relevant voltage operated Ca^{2+} channels (VOCC) of the $Cav_{1.2}$ family, also known as the long acting L-type Ca^{2+} channels. Due to the mechanism of membrane depolarization, this form of cellular activation has been termed electromechanical coupling. In contrast, single unit smooth muscles have very little innervation and are primarily activated by autocrine and paracrine hormones, including noradrenalin, adrenalin, and angiotensin II, all of which function through G-protein coupled membrane receptors. Receptor activation either triggers sarcoplasmic reticulum-mediated Ca^{2+} release or membrane

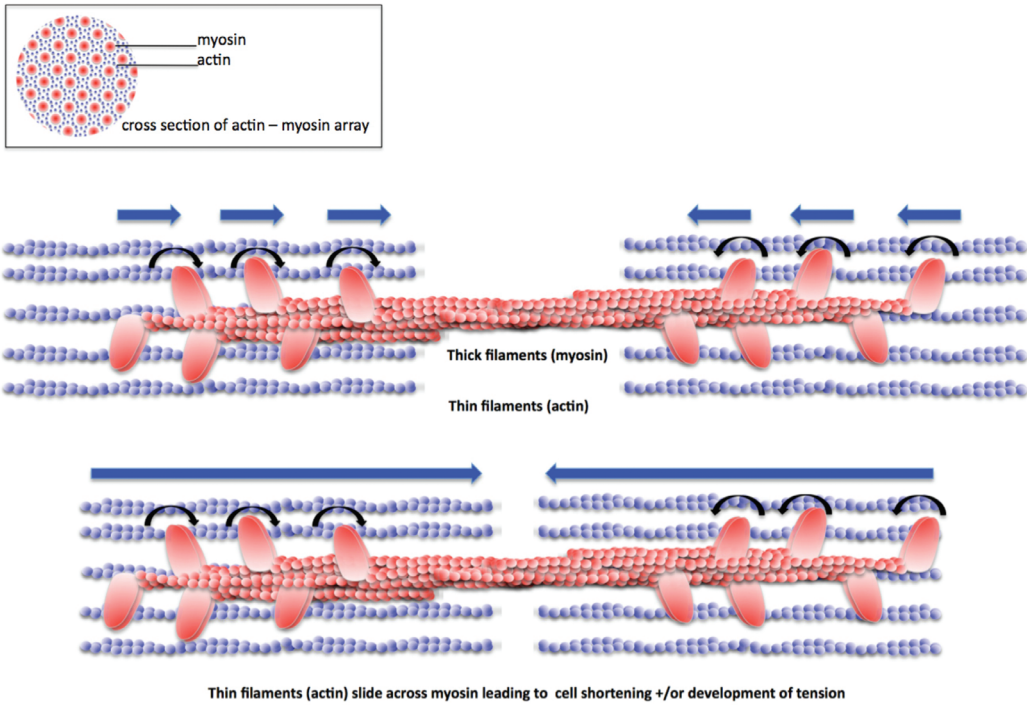

FIGURE 2.2: Illustrates the patterned array of actin and myosin in smooth muscle in both cross section and the longitudinal axis. Following phosphorylation of the light chains of myosin, actin and myosin interact followed by the synchronous sliding of actin across the myosin. The movement of actin filaments toward the center of the cell is driven by the Mg^{2+} ATPase activity in the myosin heads and results in cell shortening or development of tension.

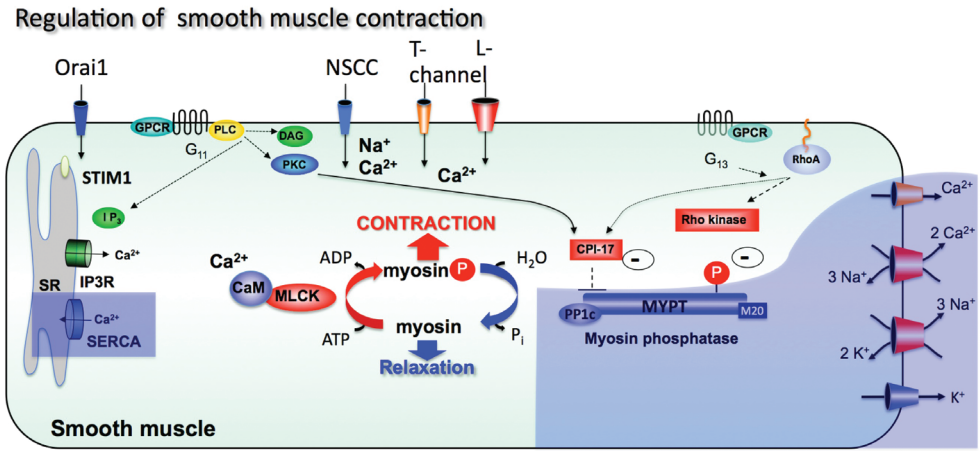

FIGURE 2.3: Illustrates the major pathways by which Ca^{2+} enters the cytosol, areas highlighted in blue indicate mechanisms by which Ca^{2+} exits that cell. Ca^{2+} entry activates Ca^{2+} CaM-dependent myosin light chain kinase leading to phosphorylation of myosin, leading to actin myosin interaction and contraction. Myosin phosphatase dephosphorylates myosin uncoupling actin-myosin favouring vasorelaxation. Various G-protein coupled receptors are capable of activating PKC/CPI-17 or RhoA/Rho kinases pathways which are capable of inhibiting myosin phosphatase further favouring vasoconstriction.

depolarization through the activation of ion channels which may include VOCC. Consequently this form of activation has been termed pharmacomechanical coupling. Experimental evidence also exists to suggest that like striated muscle, extracellular Ca^{2+} entry in smooth muscle can also activate SR Ca^{2+} release into the cytosol, so called Ca^{2+} induced Ca^{2+} release, although this appears to be a less common mechanism of Ca^{2+} entry. Once activated, single unit smooth muscle cells tends to contract in synchrony with neighbouring smooth cells, which are coupled through gap junctions. Gap junctions are composed of 6 connexin proteins, which are transmembrane spanning proteins which assemble to form a barrel-shaped connexon or hemichannel in the plasma membrane. When two hemichannels from adjacent cells assemble they form a functional gap junction that enables the movement of ions (electrical coupling) and small molecules between adjacent cells (Figure 2.1). Evidence indicates that at least some of the vascular smooth muscle cells in most vascular beds are electrically coupled via gap junctions and may even be coupled to the endothelium in a similar manner.

SMOOTH MUSCLE FUNCTION

As with other muscle types smooth muscle functions best when at its optimal resting length L_0, which provides the ideal balance of actin-myosin interaction and muscle shortening. Vascular smooth muscle cells that are stretched beyond L_0 have less than optimal overlap of actomyosin crossbridges and thus are unable to maintain or generate maximum force. In contrast, smooth muscle that is over shortened experiences increased internal resistance due to internal friction generated from having too many slowly cycling cross bridges. However, in smooth muscle the optimal length tension relationship is considerably more variable than that for skeletal or cardiac muscle, but appears to be directly related to the degree of phosphorylation of the regulatory light chains of myosin. The broader range of optimal resting length amongst smooth muscle may reflect the dynamic changes in load that exist within the vasculature and of the high actin:myosin ratio in smooth muscle relative to striated muscle. Interestingly, at the onset of stretch or pressurization smooth muscle responds via activation of stretch receptors (TREK and TRAK) that induce Ca^{2+} entry and consequent smooth muscle shortening, which directly offsets increased vascular wall stress. This is the important mechanism governing the phenomenon of autoregulation. It is important to note that although gastrointestinal smooth muscle appears relatively unaffected by significant stretch, more that 25% stretch often destroys the contractile properties of vascular smooth muscle.

MYOFILAMENT BASIS OF SMOOTH MUSCLE CONTRACTION AND RELAXATION

Motility studies using isolated actin and myosin proteins have identified that the duty cycle of the myosin head power stroke is 7-11 nm. Perhaps more important than the stroke length of the myosin is the activity of the myosin ATPase, which along with Ca^{2+}/CaM and the activation state of myosin light chain kinase and myosin light chain phosphatase, determines the extent and the rate of contraction of the vascular smooth muscle (Figure 2.3). Smooth muscle myosin ATPase hydrolyses ATP at a rate of ~0.16 moles ATP/mol myosin/second, which is several orders of magnitude slower than the skeletal muscle myosin ATPase which hydrolyses ~10-20 moles ATP/mol myosin/

second. In part the slower ATPase rate of the myosin head accounts for the vastly slower contraction rates of vascular smooth muscle compared with striated muscles. In addition, there are a variety of different isoforms of smooth muscle myosin II which when differentially expressed will increase or decrease the maximum rate of smooth muscle contraction. For example, so called foetal isoforms of smooth muscle myosin II have a slower rate of contraction. In addition, these "foetal" isoforms have been shown to be upregulated during extended hypoxia, and during phenotypic remodelling of smooth muscle from a contractile to synthetic or proliferative phenotype.

Smooth muscle contraction and relaxation

As mentioned, unlike cardiac and skeletal muscle, smooth muscle does not contain troponin and therefore is not subject to troponin mediated regulation of contraction. Smooth muscle contraction makes use of another Ca^{2+} binding protein called calmodulin (CaM), which when bound with Ca^{2+} mediates the activation of the actin bound myofilament enzyme, myosin light chain kinase (MLCK), which in turn phosphorylates the regulatory light chains of myosin (LC_{20}). Phosphorylation of the myosin LC_{20} is a critical step in smooth muscle contraction which causes a conformational change in the myosin head enabling the interaction of myosin with actin, cross bridge cycling, and contraction. Removal of cytosolic Ca^{2+} occurs through the activation of energy dependent plasma membrane Ca^{2+} ATPases (PMCA), Na^+/Ca^{2+} exchangers and sarco/endoplasmic reticulum CaATPases (SERCA) (Figure 2.3). However, since MLCK-mediated phosphorylation of the serine 19 of myosin LC_{20} generates a covalent bond, simply removing Ca^{2+} does not directly cause vasodilatation. However, myosin associated, myosin light chain phosphatase (MLCP), is responsible for the dephosphorylation of myosin LC_{20} and the consequent loss of smooth muscle acto-myosin interaction and the attenuation of cross bridge cycling (Figure 2.3). It is important to recognize that, simple removal of extracellular Ca^{2+} only stops the phosphorylation of LC_{20} and does not provide an explanation for subsequent smooth muscle relaxation since the LC_{20} remains phosphorylated. This also partially explains why Ca^{2+} channel blockers are less effective in attenuating pre-existing vascular spasm as opposed to preventing spasm.

ION CHANNELS IMPORTANT IN THE REGULATION OF SMOOTH MUSCLE FUNCTION

Regulation of cellular Ca^{2+}

There are vast arrays of ion channels, pumps, transporters and exchangers that are important in regulating ionic balance and smooth muscle membrane potential. Perhaps the best know are the electrogenic $3Na^+/2K^+$ ATPase and the voltage gated L-type Ca^{2+} channels but includes: Na^+/Ca^{2+} exchangers, plasma membrane Ca^{2+} ATPases (PMCA), which provide routes to extrude Ca^{2+} from the cytosol into the extracellular space, whereas the sarcoplasmic reticulum Ca^{2+} ATPases (SERCA) are important in removing Ca^{2+} from the cytosol back into the SR. In contrast, when the SR becomes depleted of Ca^{2+}, Ca^{2+} sensor proteins in the SR termed stromal interacting molecule 1 (STIM1) translocate to the plasma membrane and activate an ion channel called Orai1 which enables refilling of SR Ca^{2+} stores. In addition, a great deal of recent research has focused on the non-selective cation channels of the transmembrane receptor potential canonical (TRPC) family that are thought be involved

in regulating Na^+ and Ca^{2+} entry. Finally a series of potassium channels are involved in either re or hyperpolarisation of the plasma membrane and thereby have therapeutic potential in limiting extracellular Ca^{2+} entry through voltage operated Ca^{2+} channels and thereby limiting vasoconstriction.

Sources of cytosolic Ca^{2+} entry

Within the smooth muscle cell, Ca^{2+} enters the cytosol from the extracellular space or from the intracellular endoplasmic reticulum, which in muscle cells is termed the sarcoplasmic reticulum (SR). Within muscle the sarcoplasmic reticulum has become variously modified to affect Ca^{2+} release into the cytoplasm. Typically agents that activate the ryanodyne receptor such as caffeine or phospholipase C (PLC) derived inositol 1, 4, 5 tris phosphate (IP3) which activates the IP3 receptors (which are ion channels) in the SR cause Ca^{2+} to be released into the cytosol. Ca^{2+} entering the smooth muscle cell from the extracellular space does so through non-selective cation channels or selective Ca^{2+} channels, which may or may not be gated by voltage. To date the most important source of extracellular Ca^{2+} entry in vascular smooth muscle is mediated by the voltage dependent Ca^{2+} channels (VDCC). The primary VDCC are the long lasting Ca^{2+} channel, so called L-type or $Ca_v1.2$ channels, which are the clinical targets of the L-type channel blockers the dihydropryidines, phenylalkamines, benzothiazapenes. More recent evidence indicates that a second class of VDCC, the transient or T-type Ca^{2+} channels also known as the $Ca_v3.X$ family may be important in mediating Ca^{2+} entry in the microvasculature. As the name suggests VDCC are activated by a depolarization of the plasma membrane, which increases the open probability and overall Ca^{2+} conductance into the cell. In addition, a variety of non-selective cation channels have the capacity to conduct a variety of ions including Ca^{2+} and Na^+ into the smooth muscle cell but due to their low conductance are currently thought to be more important in regulating membrane potential and subsequent activation of plasma membrane VDCC (Figure 2.3).

Potassium channels

The insulin-dependent electrogenic $3Na^+/2K^+$ ATPase is important in establishing the resting membrane potential (E_M) of the vascular smooth muscle cell. However, the activation states of several types of K^+ channels in smooth muscle are also important in effecting membrane depolarization and hyperpolarisation and consequent smooth muscle contraction and relaxation, respectively. The inward rectifier K_{IR} channels become activated when the membrane becomes hyperpolarized and beyond the equilibrium potential for potassium (E_K) they transport more K^+ ions from the extracellular space into the cell thereby offsetting or rectifying the hyperpolarizing stimulus. However, there are few if any physiological conditions in which E_M is more negative than E_K, consequently, even the K_{IR} channels conduct a small outward hyperpolarizing K^+ current, and therefore along with the $3Na^+/2K^+$ ATPase may be important in mediating smooth muscle tone.

The K_V family of potassium channels as the name suggests are activated by depolarization and thus are thought to be an important control mechanism to hyperpolarize the smooth muscle cell following neural or hormonal-mediated depolarization. Agonists including histamine acting through the H1 receptor have been shown to block the 4-aminopyridine sensitive K_V channels in coronary arteries.

Physiologically K_{ATP} channels are activated by agents including, adenosine, calcitonin gene

regulated peptide (CGRP) and vasoactive intestinal peptide (VIP). The activation of K_{ATP} channels and hyperpolarization mediated vasodilatation is thought to be due in part to activation of adenylyl cyclase and subsequent cAMP dependent activation of protein kinase A. More recent evidence has also indicated that K_{ATP} channels become activated in a protein kinase C-dependent manner. However, perhaps more important is the fact that cytosolic ATP and ADP function to close and open K_{ATP} channels, respectively. This explains part of the mechanism underlying the finding that vasculature in ischemic tissue, containing high ADP: ATP levels extrude K^+ in an effort to hyperpolarize the membrane and effect vasodilatation. Both experimentally and clinically the so-called vasodilatory K^+ channel openers including pinacidil, cromakalim, diazoxide, and minoxidil activate K_{ATP} channels. Interestingly the antidiabetic sulfonylurea drugs, including glibenclamide actually inhibit K_{ATP} channels, enabling membrane depolarization and activation of VOCC in pancreatic beta cells enabling insulin release. Consequently overuse of sulfonourea drugs may therefore interfere with the efficacy of vascular K^+ channel openers or directly contribute to vasoconstriction.

The large conductance Ca^{2+} activated potassium channels (BK_{Ca}) channels are also voltage sensitive but the smaller conductance smK_{Ca} channels are less sensitive to voltage. This family of K^+ channels are activated by increases in cytosolic Ca^{2+} which occurs after agonist stimulation, membrane depolarization or stretch/pressure-dependent activation of Ca^{2+} entry and therefore is involved in that arm of the myogenic mechanism involved in hyperpolarization.

G protein coupled receptors (GPCRs) transduce signals from the autonomic nervous system and hormonal stimuli including bradykinin, noradrenalin, adrenaline, angiotensin II, endothelin-1, serotonin and thromboxane A_2. Many GPCRs exhibit divergent subcellular signalling mechanisms and there is increasing evidence for diversity of subcellular signalling amongst vascular beds (Figure 2.3). For example, angiotensin II can be generated both locally within smooth muscle cells and systemically through the renin angiotensin system (RAS). In smooth muscle the type I AngII receptors are prototypical G-protein coupled receptors which couple through $G_{q11.}$ Similarly endothelin-1 can be generated locally via endothelial cells, inflammatory cells or renal sources. Like Ang II, endothelin-1 makes use of G_{q11} in smooth muscle to activate PLC, releasing diacylglycerol (DAG) activating non selective cation channels which facilitates membrane depolarization and subsequent extracellular Ca^{2+} entry through VGCC. In addition, the activation of PLC generates IP3 causing SR-mediated Ca^{2+} release. DAG can also activate PKC leading to the phosphorylation of CPI-17 which specifically inhibits myosin phosphatase, favouring phosphorylation of the LC_{20} of myosin and vasoconstriction (Figure 2.3). However, in contrast to AngII, endothelin-1 also activates G_{13} coupled receptors activating the RhoA/ Rho associated kinase which leads to a direct inhibitory phosphorylation of myosin phosphatase, again favouring contraction (Figure 2.3).

ENDOTHELIAL REGULATION OF SMOOTH MUSCLE VASODILATATION

Nitric oxide is a potent vasodilator generated in the endothelium which has many and varied effects in the vasculature including attenuating: platelet adhesion and aggregation, cellular proliferation, and vasoconstriction. A common theme underlying the influence of nitric oxide is activation of guanylyl cyclase, formation of cGMP,

activation of protein kinase G and consequent activation of K^+ channels effecting K^+ removal from the cell leading to membrane hyperpolarization and consequent inactivation of VDCC favoring low intracellular Ca^{2+} and vasorelaxation. Cyclooxygenase activation in endothelial cells also leads to generation of prostaglandin PGI_2 which leads to receptor mediated activation of adenylyl cyclase, generation of cAMP, subsequent activation of PKA and inhibition of K^+ channels (Figure 2.4).

SMOOTH MUSCLE PROLIFERATION AND VASCULAR REMODELLING

In the normal adult vascular wall most vascular smooth muscle cells subserve a contractile function to directly modulate vasoconstriction and vasodilatation. However, during development, following injury or in the presence of growth factors and mitogens, including inflammatory cytokines and oxidized lipids, vascular smooth muscle can undergo phenotypic modulation. Vascular smooth muscle phenotypic modulation involves a partial down regulation of the proteins that activate the contractile apparatus in favour of the synthetic and proliferative cellular machinery i.e., the cell increases the abundance of; endoplasmic reticulum, ribosomes for protein synthesis and the density of the Golgi apparatus. So called synthetic vascular smooth muscle cells are therefore able to undergo very active protein and DNA synthesis, cell division, and in pathological settings are capable of taking up large amounts of oxidized and nonoxidized lipids which can contribute to lipid loading of vascular smooth muscle cells and the formation of so-called foam cells in the vascular wall. As the name foam cell suggests, under microscopic examination lipid laden smooth muscle cells appear much like foam. Synthetic vascular smooth muscle cells also secrete, external to the cell, a great deal of extracellular matrix including the proteins; collagen I, III, IV, and the proteoglycans, perlican, hyaluronan, laminin. Proliferative smooth muscle cells also secrete or associate with the membrane surface several, matrix metalloproteinases (MMPs) and their corresponding tissue inhibitors of matrix metalloproteases (TIMPs) to enable correct repair and remodelling of growing or damaged vessels. Evidence exists that a chronic excess of inflammatory cytokines and growth factors can cause dysregulation of both MMPs and TIMPs which can contribute to inappropriate vascular remodelling. This remodelling plays a significant role in the progression of vascular stenosis, restenosis following mechanical interventions, the progression of unstable atheroma, and aneurysmal dissection and rupture.

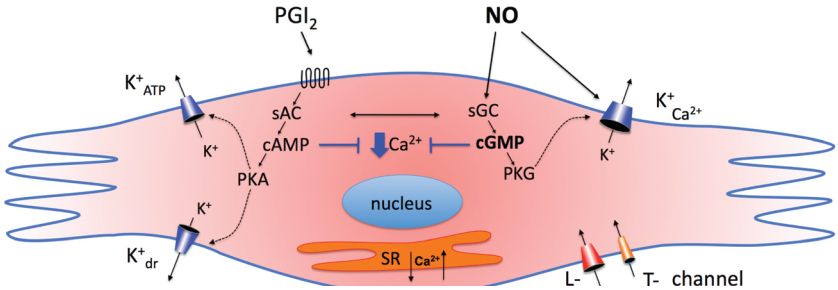

FIGURE 2.4: outlines the major influences of prostaglandin I_2 and nitric oxide (NO) in regulating the activation state of various K^+ channels leading to hyperpolarization of smooth muscle cells and vasodilatation.

At this point it is worth noting that proliferative smooth muscle cells have an attenuated response to vasoconstrictors and vasodilators, probably due to the down regulation of the contractile apparatus and certain elements of the subcellular signalling machinery that is involved in vasoconstriction. However, many of the ligands that normally lead to vasoconstriction, for example, noradrenalin, angiotensin II and endothelin also function to promote smooth muscle proliferation both in the context of cellular hypertrophy and hyperplasia. Platelet derived growth factor (PDGF), is a potent smooth muscle cell mitogen and growth stimulant and contributes to normal vessel repair while chronically elevated levels, for example, generated from unstable thrombus, can contribute to proliferative vascular disorders. Interestingly nitric oxide, in addition to functioning as a potent vasodilator also limits smooth muscle hyperplasia and hypertrophy, probably by limiting intracellular Ca^{2+} and associated Ca^{2+}dependent vascular proliferation.

SUMMARY

It is clear from the preceding that there is a dynamic interplay between cellular Ca^{2+} entry from the extracellular space mediated by membrane depolarization and the activation of voltage dependent Ca^{2+} channels. Extracellular Ca^{2+} entry can be offset by the activation of K^{+} channels through either endothelial nitric oxide-cGMP/PKG- or PGI2-cAMP/PKA-dependent mechanisms, both of which function to limit smooth muscle contraction and proliferation. However, the simple fact that L-type Ca^{2+} channel blockers and nitric oxide treatment are limited in their ability to effectively manage several disorders of hypercontractility suggests that the additional mechanisms including; SR Ca^{2+} release and regulation of myosin phosphatase are also important targets for future therapeutic development.

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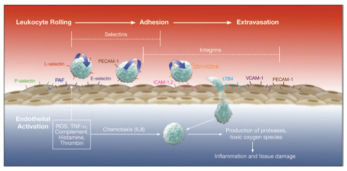

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