Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists

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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

12 • Pathogenesis of Aortic Aneurysms

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INTRODUCTION

Over the last decade aortic aneurysm has gained increased focus for a number of reasons. Firstly, the widespread use of imaging and screening in some countries has resulted in greater detection of the condition. Secondly since the condition is much more common in the elderly the number of patients with the problem is projected to increase progressively with the rising average age of the population. Surgical and endovascular treatments have not been shown to reduce mortality for patients with small abdominal aortic aneurysms (AAAs) and thus other therapies are required to deal effectively with the large group of patients being identified with small AAAs.[1,2] There is also a need to provide better prognostic information for patients with AAA by risk stratification in terms of the likelihood of complications, including AAA progression to a stage where surgery is required and also other cardiovascular complications.[3] As a result of these current management deficiencies, there has been an explosion in studies directed at improved understanding of AAA pathogenesis. These studies have mainly consisted of investigations in animal models or assessments of human DNA, tissue or blood samples.[3] Mice models have been particularly popular due to the ability to perform elegant interventions and assess their influence on AAA. Data from such studies has thus had a major impact on pathogenesis theories and treatment targets. However, animal models have limitations and cannot be expected to be completely comparable to human disease. Human AAAs develop over many decades in patients with multiple risk factors and with numerous mechanisms leading to the final common result of an AAA. In contrast rodent models usually involve techniques to induce aortic aneurysms over a few weeks or result due to single genetic deficiencies. These models have allowed considerable insight not possible with human association studies alone but their exact importance will only become evident when treatment strategies they have suggested are examined by interventional trials in patients with small AAAs.

DIFFERENCES BETWEEN THORACIC AND ABDOMINAL AORTIC ANEURYSMS

Numerous factors contribute to differences between the thoracic and abdominal aorta. In adults, the thickness and number of elastic lamellae gradually decreases along the aorta resulting in the wall thickness falling from about 1.5mm at the arch to less than 1mm in the distal abdominal aorta.[4] The fall in elastin is particularly notable in the aneurysm-prone infra-renal aorta.[5] As a result, the abdominal aorta has a smaller cross-sectional area and a stiffer wall. Compared with the thoracic aorta, the infra-renal aorta is exposed to reflected pressure waves from the iliac bifurcation, higher pulse pressures and increased wall shear stress due to its position proximal to a major bifurcation.[6] These adverse haemodynamic conditions make the abdominal aorta particularly prone to both atherosclerotic and aneurysmal disease.[7]

The propensity for aneurysm formation in the infrarenal aorta may also relate to differences in aortic smooth muscle cell lineage: cells forming the arch of the aorta are derived from neural crest; of the thoracic aorta from somite-derived cells; and of the abdominal aorta from splanchnic mesoderm.[8] Localised intrinsic aortic wall characteristics may influence a range of molecular pathways that are important in aneurysm formation – notably angiotensin II and transforming growth factor beta (TGFβ) signaling.[9] Divergent inflammatory responses may also contribute to differences between thoracic and abdominal aortic aneurysms. The more florid inflammation seen in AAAs may reflect greater vasa vasorum density and differential immune responsiveness.[10] In addition, the expression of pathogen-sensing Toll-like receptors by resident dendritic cells (resulting in differential T cell response) varies considerably, with each artery having a distinct profile.[11]

There are clear differences in the genetic factors associated with thoracic and abdominal aortic aneurysms. The importance of single gene mutations as causes of aneurysms decreases from the proximal to the distal aorta.[9] The role of common susceptibility genes has yet to be clarified. Given that aneurysms of the abdominal aorta are ~5 times more common than in the thoracic aorta, this chapter will focus primarily on AAA.

SUMMARY OF CURRENT THEORIES AND STAGES OF AAA EVOLUTION

The natural history of an AAA can be divided into initiation, progression and rupture. This concept is useful since there is evidence that the factors promoting each stage may be different.[12] Whilst understanding AAA initiation may ultimately lead to the goal of primary prevention, an understanding of AAA progression can guide the development of therapy for patients with small AAAs in an attempt to reduce expansion and rupture rates. An attempt has been made to link putative mechanisms to different stages of AAA in Table 12.1. In the subsequent sections the evidence implicating these mechanisms in AAA pathogenesis will be discussed.

ATHEROSCLEROSIS AND AAA

Patients with AAAs frequently have generalized atherosclerosis, and numerous studies show the association of coronary and peripheral atherosclerosis with AAA.[3] Whether this association between AAA and aortic atherosclerosis is causal or simply due to common risk factors is unknown. The most compelling argument for a causative role of

TABLE 12.1: Mechanisms implicated in AAA pathogenesis

Mechanism	AAA stage
Atherosclerosis	Initiation
Innate immunity	Initiation and progression
Extracellular matrix dysfunction	Initiation
Infection	Initiation
Biomechanical disturbance	All stages
Angiogenesis	Progression
Intra-luminal thrombus	Progression
Extracellular matrix destruction	All stages

atherosclerosis in AAA has been centered on arterial remodeling.[13] A large body of *in vitro*, animal, and histology data suggests that when an arterial luminal stenosis develops, compensatory changes occur in the media in response to shear stress alterations. The extracellular matrix remodeling promotes expansion of the artery in an attempt to normalize lumen diameter and shear stresses. Excessive remodeling could explain the medial thinning typically seen in AAAs. Elastin breaks stimulated by medial proteolysis and the diffusion of pro-inflammatory cytokines from inflammatory cells present within atheroma or associated thrombosis could also provide the stimulation for the chronic inflammation seen in AAAs. On the basis that atherosclerosis stimulates AAA development, all patients with AAA would necessarily have significant atherosclerosis and thus should be considered for indicated medical therapy, as currently advised by American Heart Association guidelines in which AAA is considered an atherosclerotic equivalent.[14]

An alternative theory suggests that the development of AAA and atherosclerosis are independent. Shared environmental and genetic risk factors may promote the development of both atherosclerosis and AAA in some patients, but the mechanisms involved are distinct. A third possibility is that either aortic atherosclerosis or AAA can develop first and both can subsequently stimulate the development of the other (Figure 12.1). Currently, evidence to support one of these theories over the other is largely limited to documenting similarities and differences in risk factors and findings within rodent models for atherosclerosis and AAA (Table 12.2).[3,15-19]

Further insight into the importance of atherosclerosis in AAA is of therapeutic relevance. Recent human association studies have shown conflicting results on whether drugs that are effective for atherosclerosis, such as statins or angiotensin converting enzyme inhibitors, inhibit AAA progression.[20-23]

IMMUNE MECHANISMS IN AAA

Relatively few studies have been carried out to establish the role of immune mechanisms in AAA by comparison to athero-thrombosis. Examination of biopsies removed from large AAAs demonstrate a marked inflammatory infiltrate, particularly within the adventitia. Assessment of the relative numbers of different cell types within AAA biopsies have been performed using a variety of techniques including histology, flow cytometry and genomic techniques.[24,25] These studies suggest that in end-stage human AAA, the predominant inflammatory cell types are T and B lymphocytes.[24] Other inflammatory cells are also identified, such as macrophages, dendritic cells and mast cells.[24] Current evidence implicates both innate and adaptive immunities in AAA pathogenesis.

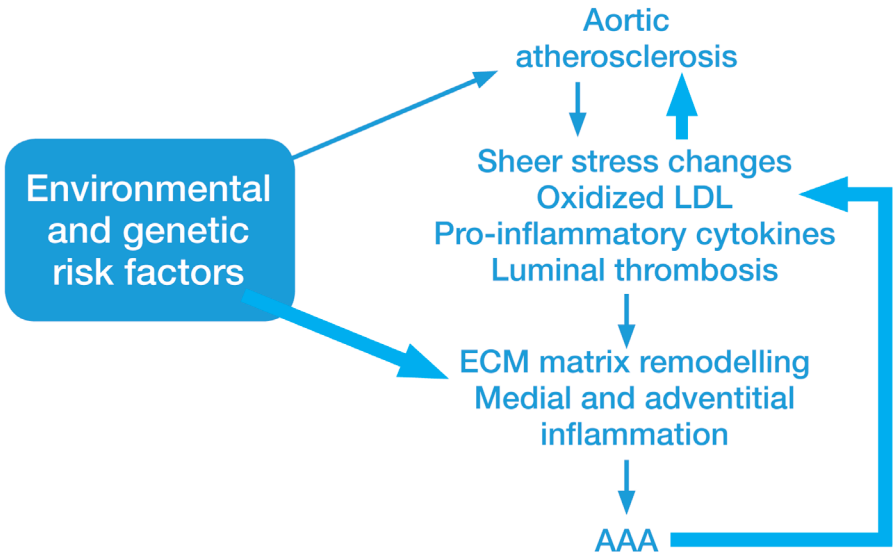

FIGURE 12.1: Theories regarding relationship between atherosclerosis and AAA. According to theory 1 (thin line + arrow), environmental and genetic risk factors lead to development of aortic atherosclerosis. Resultant positive remodeling, intimal thrombosis, and release of proinflammatory cytokines stimulate secondary matrix degradation and adventitial inflammation which promotes AAA development. According to theory 2 (thick line + arrow), environmental and genetic risk factors directly stimulate aortic medial degradation and adventitial inflammation, leading to AAA formation, which secondarily stimulates intimal atherosclerosis. More likely, both pathways act to some extent, with the relative proportion varying from patient to patient depending on the risk profile. ECM indicates extracellular matrix; LDL, low-density lipoprotein.

T cells, including both $CD4^+$ and $CD8^+$ cells, are probably the best-studied inflammatory cells in human AAAs. T cells may be demonstrated in both the adventitia and media of human AAA biopsies (Figure 12.2). The high numbers of T cells in human AAA may reflect both increased influx and also reduced clearance of these cells. T cells isolated from human AAAs are more resistant to apoptosis than those from healthy donors or patients with aortic occlusion disease (AOD).[26] Different subsets of T cells may play varying roles in AAA. For example $CD4^+CD31^-$ cells have been implicated in AAA progression by enhancing $CD8^+$ cell-mediated vascular smooth muscle cell (VSMC) cytolysis and macrophage-derived matrix metalloproteinase (MMP)-2 and -9 production.[27] Compared with healthy aortic tissues, AAAs also contain higher numbers of $CD69^+DR^+$ active T cells with lower expression of adhesion molecule CD62L,[28] although the potential antigens that activate T cells remain undiscovered.

The role of T helper (Th) cells in human AAA is controversial. According to some reports a significant percentage of freshly isolated T cells express markers of a Th1 immune response.[29] Furthermore cytokines associated with Th1 immune responses are elevated in the blood and aortic tissue of patients with AAA.[30] In the $CaCl_2$ AAA mouse model, absence of CD4 or Th1 cytokine IFN-γ suppressed AAA formation.[31] In contrast, several groups report different observations. These include high concentrations of Th2 cytokines IL4, IL5, and IL10, but negligible Th1 cytokines IL2 and IL15 in AAA biopsies.[32] In mice major histocompatibility complex

TABLE 12.2: Some similarities and differences between atherosclerosis and AAA.

Characteristic	Similarities	Differences
Clinical risk factors	Smoking, hypertension, and obesity are common risk factors for AAA and aortic atherosclerosis.[3]	Diabetes is a negative or neutral risk factor for AAA but important risk factor for atherosclerosis.[3] Male gender and smoking are much more dominant risk factors for AAA than atherosclerosis.[3]
Circulating risk factors	AAA and atherosclerosis have many similar biomarkers, e.g. fibrinogen, CRP and HDL (negative).[15]	There are a number of disparate markers for AAA and atherosclerosis, e.g. LDL has no clear association with AAA but is an important risk factor for atherosclerosis.[16]
Genetic risk factors	Family history is an important risk factor for both AAA and atherosclerosis.[3] A locus on chromosome 9p21 is associated with CHD, stroke and AAA.[17]	Some recognised genetic determinants of atherosclerosis have no consistent association with AAA, e.g. Apolipoprotein E single nucleotide polymorphisms.[18]
Histology	Intimal atheroma and thrombosis are usually present in both AAA and atherosclerosis.[3]	Marked elastin fragmentation and adventitial chronic inflammation is mainly restricted to AAA.[3]
Rodent models	Some mice (e.g. Apolipoprotein E deficient) prone to atherosclerosis are also more sensitive to AAA induction.[3] Interventions protective from AAA frequently also reduce atherosclerosis.[3]	There are examples of differential effects of interventions on AAA and atherosclerosis progression, e.g. TNF and MMP-12 deficiency.[19]

mismatched aortic transplants develop an immune response dominated by IL4. These transplanted aortas develop severe inflammation, elastin degradation, marked MMP-9 and MMP-12 expression, and AAA. These AAAs can be prevented by anti-IL4 antibody or by concomitant IL4 mutation.[33] Overall it is possible from current data that both Th1 and Th2 responses are involved in AAA pathogenesis.

Macrophages, neutrophils, and mast cells have also been implicated in AAA formation. Macrophages are demonstrated within the adventitia and media of human AAA biopsies (Figure 12.2). Human AAA biopsies contain significantly higher levels of total neutrophil elastases, localized in the adventitia and thrombus than aortic tissue from patients with AOD or without significant disease.[34] Neutrophil recruitment to AAAs may be mediated by complement components C3a and C5a or neutrophil-derived IL8 and leukotriene B4.[35,36] Antagonism of C3a and C5a blocked AAA formation in a mouse model.[35] Antibody depletion of neutrophil protected mice from elastase induced AAA development.[37] Diminished neutrophil recruitment to the elastase-injured aortic wall due to dipeptidyl peptidase I-deficiency impaired AAA formation. This protection was lost when wild type normally functioning neutrophils were restored in these mice.[38] All these data support a role for neutrophil in AAA formation and progression in mice models.

Small numbers of mast cells are found within the outer media and adventitia of human AAA (Figure 12.2) and the cell

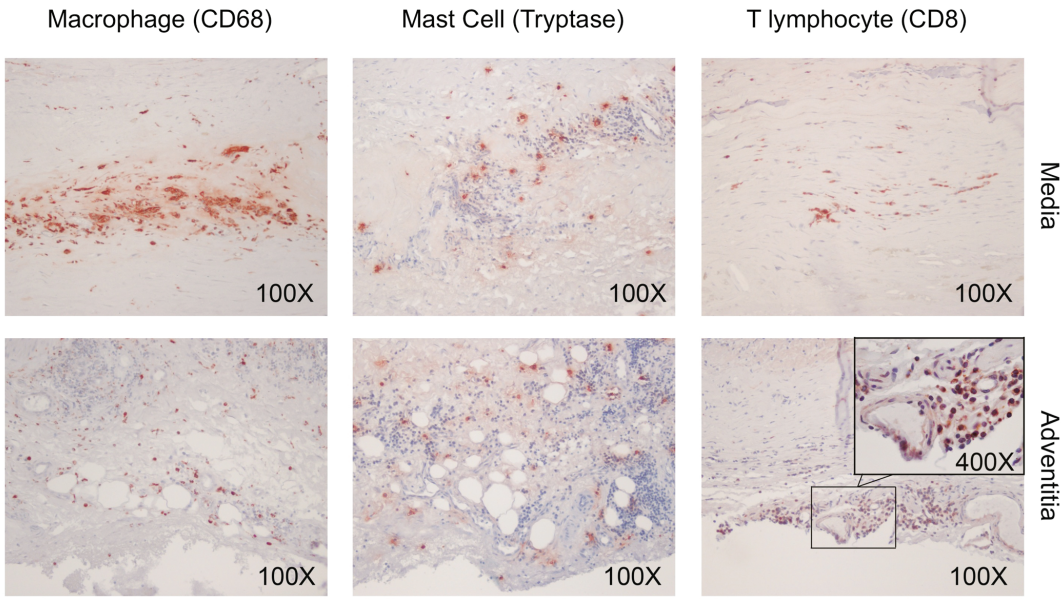

FIGURE 12.2: Example of assessment of inflammatory infiltrate in a human AAA biopsy. Macrophages, mast cells and CD8+ T cells within the media and adventitia of human AAA biopsies. Rabbit anti-human CD8 monoclonal (1:75, Abcam, Cambridge, MA), mouse anti-human CD68 monoclonal (1:60, Dako, Carpinteria, CA), and mouse anti-human tryptase (1:1500, Chemicon International, Inc., Temecula, CA) antibodies were used to detect $CD8^+$ T cells, macrophages, and mast cells in paraffin sections.

number has been correlated with AAA diameter.[39] Neovessel area within biopsies of human AAAs is also correlated with mast cell number. In rats, peri-aortic $CaCl_2$ injury induces AAA with associated increase in aortic mast cell content. Mast cell-deficient rats (*Ws/Ws*) or those that received mast cell inhibitor tranilast were protected from AAA formation. This effect was associated with reduced inflammatory cell infiltration, MMP-9 activity, angiogenesis and elastin degradation.[39] Similar observations were demonstrated in mast cell-deficient ($Kit^{W\text{-}sh/W\text{-}sh}$) mice.[40] In an aortic elastase perfusion-induced AAA model, absence of mast cells protected mice from AAA, whilst pharmacological mast cell stabilization with an anti-allergy medicine cromolyn significantly inhibited AAA expansion.[40] The findings suggest the intriguing possibility that mast cell stabilizing agents may be able to slow AAA progression.

EXTRACELLULAR MATRIX DYSFUNCTION

Examination of biopsies of large human AAAs indicates marked medial thinning and deficiency of VSMCs as consistent features.[3] In human AAA lesions, the best-studied extracellular matrix (ECM) proteins include elastin and collagen. Loss of functional elastin is an important feature of human AAA and may be a more generalized feature of arteries of patients with aneurysms.[41] Disruption of elastin has been particularly implicated in AAA development and progression, while degradation of collagen is thought to be more important in AAA rupture.[42] The availability of knock-out mice models has allowed the dissection of some of the mechanisms by which the extracellular matrix might influence AAA development. These studies suggest that extracellular matrix elements play more than just a structural role. Studies

in fibrillin-1 deficient mice suggested that the loss of this extracellular protein led to alteration in the bioavailability of TGFβ. The marfan-like phenotype stimulated by fibrillin-1 deficiency could be inhibited by using a neutralizing antibody to TGFβ.[43] Deficiency of other extracellular matrix proteins such as fibulin-4 has also been suggested to alter TGFβ signaling.[44] The mechanism by which alterations of TGFβ promotes AAA in these pre-clinical studies is currently controversial since the effects of blocking this cytokine varies in different models.[43,45] The most detailed study to date suggests that at least in one model TGFβ protects against aortic aneurysm formation by inhibiting monocyte-macrophage based tissue destruction via MMP-12 production.[45]

INFECTION

The development of aneurysms in which infection is a primary pathogen is well documented albeit rare. It has also been suggested that infection could play a more general role in aneurysm formation and progression. *Chlamydia pneumonia* in particular has been investigated for a role in AAA.[46] Evidence of previous *C. pneumonia* infection has been demonstrated in some patients with AAAs although the frequency of this varies due to the different methods of detection used. Conclusive evidence of *C. pneumonia* infection in a large series of patients with AAA compared to controls is currently lacking. Serological evidence of *C. pneumonia* infection has been related to more rapid AAA expansion. These findings stimulated two small trials involving a total of 124 patients to examine the influence of short course antibiotic therapy on AAA progression.[46] These studies both suggested a reduction in AAA growth over a short follow-up period but do not appear to have generated enthusiasm for larger studies directed at *C. pneumonia* eradication.[46] There are however two large on-going trials of doxycycline therapy in patients with AAA although the rationale for this therapy is based on MMP inhibition rather than antibiotic properties.

BIOMECHANICAL FORCES

One of the suggested reasons for the focal nature of AAA formation has been the variation in haemodynamic forces throughout the aorta.[7] Hypertension is a risk factor for AAA in human population studies and in rodent models it promotes AAA formation.[3,47] Focal increases in shear stress and wall strain have been demonstrated to inhibit AAA development in rodents due to reduction in macrophage induced oxidative stress.[48] These findings have in part been the stimulus for a current randomized trial examining the effect of supervised exercise in patients with small AAAs. Results from this trial are expected in 2012. Biomechanical forces may also have a role to play in the development of aortic rupture.

ANGIOGENESIS

New vessel formation has been demonstrated within the adventitia of human AAA biopsies and implicated in promoting influx of inflammatory cells.[49] In the angiotensin II induced mouse model, vascular endothelial growth factor promoted, and an angiogenesis inhibitor attenuated, AAA formation.[50,51] Of possible relevance to human therapy, simvastatin has been shown to inhibit angiogenesis in the same AAA pre-clinical model.[52]

INTRA-LUMINAL THROMBUS

Intra-luminal thrombus is a usual finding in large AAAs but rare in aneurysms situated at

more proximal sites in the aorta. The volume of thrombus is closely correlated to the size of the AAA suggesting that the thrombus could simply be a result of the changes in flow pattern due to aortic dilatation.[53] The thrombus is the likely source of a range of biomarkers which have been associated with AAA, such as fibrinogen degradation products including D-dimer.[54] These thrombus products maybe of diagnostic and prognostic value for AAA.[54] The thrombus has been demonstrated to contain large numbers of neutrophils, MMPs and cytokines.[55,56] Furthermore in a rodent model of AAA, inhibition of platelet activation has been shown to slow AAA progression.[55] In one cohort of patients with small AAAs aspirin prescription has been associated with reduced AAA progression.[57] Trials of the efficacy of anti-thrombotic therapies in reducing AAA progression and perhaps reducing other complications of AAA may follow in the near future.

EXTRACELLULAR MATRIX PROTEOLYSIS

The ECM in the healthy aortic wall is balanced by controlled biosynthesis and destruction. Either impaired production or enhanced degradation of ECM may promote AAA formation. Seeding of syngeneic rat VSMC stabilizes experimental AAAs[58] and this effect is enhanced by adenoviral expression of TGF-β.[59] Biosynthesis of collagen and elastin is regulated at both expression and post-translational modification. The latter is catalysed by poly-4-hydroxylase, procollagen lysyl hydroxylase (PLOD) and lysyl oxidase (LOX). Disruption of the LOX gene in mice leads to AAA formation and rupture.[60] LOX expression is reduced in AAA prone mice and in experimental AAA.[61] A PLOD mutation in humans predisposes to arterial rupture.[62] Adenoviral expression of exogenous LOX inhibits AAA in circumstances where endogenous LOX activity is suppressed.[63] In a rat $CaCl_2$ model, peri-adventitia delivery of an aortic elastin binding polyphenol and stabilizer pentagalloyl glucose inhibited elastin degradation and attenuated AAA expansion, without modifying inflammation, calcification, and high MMP activity. The polyphenol protected elastin from proteases induced degradation.[64] Excessive ECM accumulation may also play a detrimental role in AAA. This theory was supported by studies in Apolipoprotein E deficient (*Apoe*$^{-/-}$) mice which express collagenase-resistant mutant collagen. These mice develop increased interstitial collagen accumulation, aortic wall stiffness, susceptibility to mechanical failure and increased AAA development after angiotensin II infusion.[65]

ECM proteolysis in human AAA may be mediated by virtually all classes of proteases – MMPs, cysteine proteases cathepsins, and serine proteases that are derived from inflammatory or vascular cells after stimulation with cytokines (Figure 12.3). MMPs have been most studied. MMP-2, 3, 7, 12 have elastinolytic activity and MMP-2, 3, 7, 8, 9, 13, 14 demonstrate collagenolytic activity.[66] Studies of human AAAs biopsies suggest that a range of MMPs are upregulated, while concentrations of tissue inhibitors of metalloproteinase (TIMPs) are reduced.[67,68] It is postulated that inflammatory cells secrete MMPs and stimulate vascular cells to express MMPs in addition (Figure 12.3). In experimental AAA there is an inverse correlation between the number of inflammatory cells, neovessels and aortic wall collagen and elastin.[69] Mice in which MMP deficiency is introduced are protected from AAA induction.[70-72] Similarly seeding of VSMC which express high levels of the MMP inhibitor TIMP-1 into aortas of an experimental model of AAA prevented aortic rupture.[73] These findings implicate MMPs in

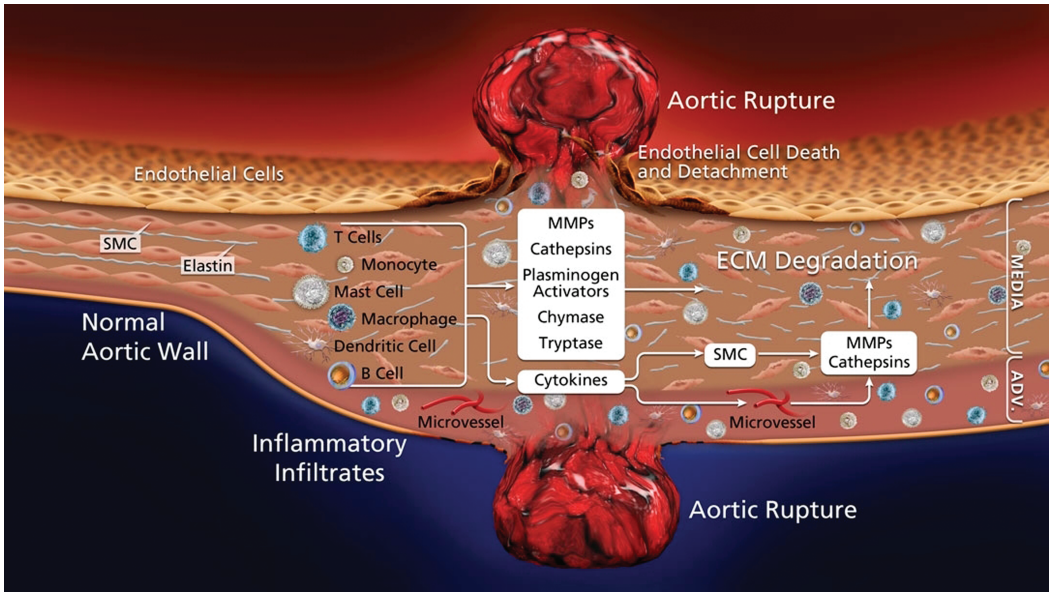

FIGURE 12.3: Schematic diagram summarizing the involvement of inflammatory cell infiltration and proteases in human AAAs. MMPs, cathepsins, plasminogen activators, chymases and tryptases are the best-studied proteases in AAA. Inflammatory infiltrates are the main sources of these proteases. Furthermore, these inflammatory cells also produce cytokines to stimulate VSMC and endothelial cells to release MMPs and cathepsins.

the development, progression and rupture of AAAs.

Increased expression of the cysteinyl cathepsins S, L, and K and decreased concentrations of their endogenous inhibitor cystatin C has previously been reported in human AAA biopsies.[74,75] Recent quantitative analysis suggested that cathepsins B, H, L, and S activities were increased by 376%, 191%, 223%, and 20% in biopsies of human AAA compared to AOD.[76] The effect of this excess cathepsin activity is currently controversial. In the elastase perfusion model, deficiency of cathepsin C, also called dipeptidyl peptidase I, reduced neutrophil infiltration and AAA expansion.[38] In contrast, *Apoe*$^{-/-}$ mice lacking cystatin C developed significantly enlarged AAAs compared with control mice.[77]

The serine proteases urokinase and tissue-type plasminogen activator (uPA and tPA) have received considerable interest in AAA research. Plasma tissue plasminogen activator has been compared in subjects with and without AAA in 5 studies.[15] Only one of the studies reported significantly higher concentrations in patients with AAA. A local role for serine protease in AAA may be more plausible than a systemic one. Absence of uPA in *Apoe*$^{-/-}$ protected mice from angiotensin II induced AAA.[78] Intra-adventitial introduction of an adenovirus over-expressing plasminogen activator inhibitor-1 (PAI-1) completely prevented AAA formation in *Apoe*$^{-/-}$ mice infused with angiotensin II. Local delivery of this virus two weeks after angiotensin II infusion prevented further expansion of small AAAs, but had no significant effect on larger AAAs.[79]

Mast cell chymase has also recently been implicated in AAA formation. In human AAA, increased chymase expression within the media and adventitia has been reported.[80] Mice with deficiency of chymase are protected from elastase induced AAAs.

In mice, chymase enhances the expression and activities of cysteinyl cathepsins, and promotes aortic elastin degradation, angiogenesis, and VSMC apoptosis.[80] Oral administration of the chymase inhibitor NK3201 (30mg/kg/day) significantly suppressed the severity and expansion of AAAs in the angiotensin II induced aneurysm model.[81] Similar observations have been reported in dogs where the chymase inhibitor NK3201 (1mg/kg/day, p.o.) inhibited AAA.[82]

Pharmacological inhibition of proteases has been widely investigated in animal models. Most of these studies focus on inhibition of MMP activity. Both MMP inhibitors BB-94[83] and doxycycline[84-86] are effective in preventing animal AAA formation. Oral treatment (100mg/kg/day) or peri-aortic perfusion of doxycycline (0.75 to 1mg/kg/day) inhibited elastase induced AAA in mice. Overall doxycycline has been shown to inhibit AAA in experimental models in >10 studies supporting the potential of this approach in human AAA.[3] In a recent trial 60 patients awaiting open AAA repair were randomized to a control group or low, median or high doses of doxycycline (50, 100, 300mg/day) for two weeks. Overall AAA biopsies from patients receiving doxycycline had reduced aortic wall neutrophil and $CD8^+$ T cell infiltration; reduced pro-inflammatory cytokine and MMP concentrations; and increased TIMP-1 and cystatin C concentrations.[87,88] Doxycycline appeared to be well tolerated with no major adverse events reported. However, a previous double blinded trial of low dose doxycycline (100mg/d) given one month prior to open AAA surgery reported no effect of the medication on MMP or TIMP expression.[89] Two randomized trials are underway examining the effect of oral doxycyline on small AAA progression.

GENETICS

Family history is a risk factor for all types of aortic aneurysms. Up to 20% of thoracic aortic aneurysms are in individuals with a familial preponderance and the understanding of the genetics of aneurysms at this site is advancing rapidly. Approximately 5% of thoracic aortic aneurysms occur in patients with well defined monogenetic connective tissue diseases, such as Marfan syndrome (mainly due to mutation in fibrillin-1).[90] Recently a range of further mutations have been identified in genes associated with thoracic aortic aneurysm, including TGFβ receptor type I and II, myosin-11 and alpha 2 actin, and aortic smooth muscle.[90] It appears likely that genetic inheritance plays a more significant role in aneurysms which develop in the ascending aorta by comparison to the abdominal aorta. Recent evidence for example suggests that the role of TGFβ receptor mutations in the development of AAAs appears to be less clear cut than described for the ascending aortic aneurysms.[91,92] It is possible that genes predisposing to AAA may have more comparability with those associated with atherosclerosis. A site on chromosome 9 originally identified in a whole genome association study for coronary heart disease has now been repeatedly associated with AAA.[17,93] Current evidence suggests that multiple genetic loci have a small effect in increasing the risk of AAA, depending on the exposure of patients to environmental or other complex risk factors, such as smoking, diet and other health behaviours. Meta-analysis of current small studies suggest that contributing genes include angiotensin converting enzyme, angiotensin type 1 receptor, methyltetrahydofolate reductase and MMP-3.[12,94]

AAA RUPTURE

Recent elucidation of the biological processes causing aneurysm development and expansion has led to translational research investigating the use of novel pharmacotherapeutic agents aimed at retarding aneurysm growth. In contrast to the expansion of AAA, the biological processes initiating aortic aneurysm rupture have received little attention. AAAs were traditionally considered to be a simple biomechanical problem, resulting from irreversible structural damage to the aortic wall that results in weakening, dilatation and eventual rupture when wall stress from the circulation exceeds the tensile strength of the wall. Focusing on aortic wall stress as the cause of rupture has led to a simplistic view that the natural history of AAAs is regulated solely by biomechanical factors. Just as the complexity of the atherosclerotic plaque has become apparent, it is now recognised that rupture of an AAA is a multifaceted biological process involving biochemical, cellular, haemodynamic and proteolytic influences.[95]

Biomechanical factors in aneurysm rupture

In a search for a more specific clinical parameter than diameter alone, biomechanical investigations have tried to predict aneurysm rupture as a function of wall stress. Several investigators revealed that ruptured or symptomatic AAAs had a significantly higher peak wall stress compared to asymptomatic AAAs, independent of blood pressure or AAA diameter. In addition, these in vivo measurements of peak wall stress using finite element analysis (FEA) predicted rupture risk more accurately than the Law of Laplace.

There are several limitations to the finite element analysis reported in these studies that assume the homogenicity of structure and thickness of the aortic wall and do not account for intraluminal thrombus. In a recent review McGloughlin and Doyle[96] suggest that aortic rupture cannot be predicted by wall stress alone and that wall strength is equally important. These authors suggest that biomechanical analysis has an increasing role to play in aortic research but that a numerical biomechanical risk index is some way off.

The role of enzymes in AAA rupture

Ex vivo mechanical testing of healthy and aneurysmal abdominal aortic wall specimens revealed that the failure strength of a typical AAA wall was lower than that of non aneurysmal aorta. The mechanism for aneurysmal wall weakening is unknown but it seems likely that the increased local production of enzymes capable of degrading elastin and interstitial collagen alters the structural integrity and predisposes the aortic wall to weakening. The earliest experimental work on AAA rupture was by Dobrin *et al* in 1984 who investigated the proteolytic effects of purified collagenase and elastase. Treatment with collagenase caused the blood vessels to dilate, become more compliant and rupture. In contrast, treatment with elastase caused the vessels to dilate markedly and become stiffer (probably due to recruitment of previously unstretched collagen fibres) but was not related to rupture. These findings have fostered the notion that elastin degradation is a key step in the development of aneurysmal dilatation but that collagen degradation is ultimately required for aneurysm rupture.

The pathological processes associated with the natural history of aneurysms to dilate and rupture are not well documented in clinical studies. Wilson *et al* found no significant differences in MMP levels in the AAA sac of large (>6.5cm) and medium (5-6.5cm) sized

aneurysms, or ruptured and non-ruptured AAA sac. When the same group analysed paired samples of aortic sac obtained from the anterior sac and the site of rupture in MMPs-8 and -9 were significantly higher at the site of rupture than in the anterior sac.[97] Aortic rupture is therefore likely caused by localised elevations in proteolytic enzymes and focal wall weakening. This concept of localised 'hot spots' of MMP hyperactivity was supported by Vallabhaneni *et al*, who demonstrated marked heterogeneity of tensile strength and MMP activity in the aneurysmal aortic wall.[98]

Role of intraluminal thrombus in aneurysm rupture

Intraluminal thrombus (ILT) is found in about 75% of all AAAs. Some authors have suggested that rupture is associated with growth of thrombus in the aneurysm, whilst there is evidence that larger AAA thrombus load is associated with a higher growth rate. Acute hemorrhage seen in the mural thrombus of patients with ruptured AAAs has led others to suggest that blood entering thrombus may have a role in rupture. There is some suggestion that AAAs with thick ILT also had increased cytokine concentrations, greater inflammation, and lower tensile strength. It was postulated that ILT, by creating a hypoxic environment may lead to compensatory inflammatory response, increase in local proteolytic activity of the wall, local wall weakening and subsequent rupture.

Investigations have demonstrated that the thrombus lining an aneurysm is an active and complex biological entity, containing many inflammatory cells, including macrophages and neutrophils. The ILT is a site of proteolytic enzyme release and activation, and it may be that mural thrombus acts as a source of proteolytic enzymes by aggregating platelets, trapping circulating cells and adsorbing plasma components.

In the future it is hoped that research into the mechanism of aortic rupture will integrate biomechanical and basic science research pathways. There is considerable evidence from isolated systems that shear and wall stress can influence the behaviour of biological processes. Understanding the interaction of these processes in the large aneurysm is key to unraveling the mechanisms of aortic rupture.

FUTURE RESEARCH

The understanding of mechanisms important in AAA is expanding rapidly within pre-clinical models. This however has not currently been matched by large trials to examine the role of therapies targeting these pathways in patients. Such trials are urgently needed given the paucity of aneurysm specific medications currently available. It is hoped that over the next decade a number of agents efficacious in slowing AAA progression and reducing other AAA specific complications, such as the high rate of cardiovascular events in these patients will be identified.

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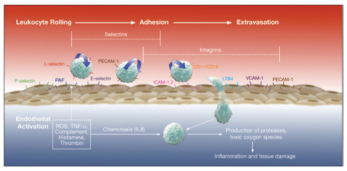

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