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Targets for medical therapy to limit abdominal aortic aneurysm progression

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Running Title – Emeto- Drug development in abdominal aortic aneurysm

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Key words- abdominal aortic aneurysm, pharmacotherapy, clinical trial, and animal models

Abstract

Abdominal aortic aneurysm (AAA) is an important cause of mortality in older adults. Most AAAs are asymptomatic and screening programs have been introduced to identify AAAs at an early stage in some countries. There is currently no accepted therapy for early stage or small AAAs, which are frequently identified by such programs. In this review we discuss work underway to identify targets for medical treatments to limit progression of small AAAs. Specifically we discuss studies, which have examined the potential of targeting inflammation, proteolysis, the renin angiotensin system, the coagulation system and sex hormones on AAA pathogenesis. As yet none of the treatment targets have translated into an agent, which can effectively reduce AAA progression in clinical practice.

1. Introduction

Abdominal aortic aneurysm (AAA) is a common degenerative disease of the aorta particularly affecting people aged > 65 years.(1-4) AAA is usually asymptomatic unless rupture occurs which is frequently fatal.(1, 2) AAA is also associated with a higher risk of other major cardiovascular events.(5) It has been reported for example, that over 45% of patients with small AAAs die secondary to myocardial infarction and stroke.(6) The primary focus of treatment is to prevent AAA rupture since this is the main recognised complication of this problem. Aortic dilatation is usually progressive and there is an absence of effective medications to limit aneurysm progression.(5, 7) Current guidelines indicate that patients with large AAAs (>50-55mm) should be considered for endovascular or open surgical repair.(7, 8) In patients with smaller AAAs, where surgical intervention is not recommended, regular clinical review and ultrasound monitoring of aortic diameter is recommended because of the lack of approved effective non-surgical interventional options for the disease.(9) Up to 60% of small AAAs undergoing monitoring expand to a size requiring surgical repair.(5, 10, 11) The development of medications that can effectively limit the number of patients requiring AAA surgery would have potential patient and cost benefits. In this article we outline current progress in developing pharmacotherapy for AAA.

2. AAA Pathology

AAA is generally accepted to be a complex disease due to aberrant interactions between environmental risk factors and genetic predisposition which exacerbate the normal ageing processes.(5) Once initiated, AAA is characterised by a number of key features. These include significant remodelling and degradation of the extracellular matrix (ECM) by proteolytic enzymes such as matrix metalloproteinases (MMPs),(12, 13) significant reductions in vascular smooth muscles (VSMC) density(14, 15) and chronic inflammation denoted by invasion of the *tunica media* by macrophages and mononuclear lymphocytes.(16-21) Intraluminal thrombus (ILT) and vascular calcifications are usually associated with AAA and have been implicated in AAA formation,(22, 23) progression,(24-27) and rupture.(18, 27-31) Localised hypoxia and increased wall stress have been reported within areas of the aorta covered by ILT.(32) Neutrophil gelatinase associated lipocalin (NGAL) found in all layers of ILT,(30)is reported to prevent MMP-9 inactivation,(33) and the NGAL-MMP-9 complex has been suggested to encourage the proteolytic degradation of the ECM.(30) ILT promotes the migration of inflammatory cells such as neutrophils(30), macrophages and T-lymphocytes,(18) which can potentially promote VSMC apoptosis and thinning of the aortic wall.(18) This presence of effector immune cells and their products together with observed immunoreactivity of IgG purified from AAA tissue to ECM proteins suggests an autoimmune aspect to AAA formation.(5, 34, 35) However, once triggered, alterations within the aortic wall most likely continue in a vicious cycle ending in progressive loss of normal ECM configuration and phenotypic modulation of VSMC.(36)

Because of the difficulty associated with obtaining human AAA tissue biopsies (most patients undergo endovascular aneurysm repair rather than open surgery),(37) and the fact that these biopsies are usually

obtained at the end-stage of disease progression, much of the knowledge gained about AAA has been obtained from animal models.(38, 39) In some cases, investigations have been supplemented by using explant culture of human samples.(1, 40-42) The animal models and the *ex-vivo* studies have been used extensively to screen putative therapeutic targets for AAA.(1, 41, 43-46)

3. Putative therapeutic strategies

A number of therapeutic strategies for AAA have been researched in both pre-clinical and clinical studies in the past decade (Figure 1). These include investigations into pathways implicated in AAA pathogenesis such as the renin-angiotensin system (RAS), inflammatory pathways, intracellular signalling pathways, and agents known to affect some or all of the aforementioned processes such as sex hormones, cholesterol lowering agents, protease inhibitors, immune cell modulators and anti-platelet therapy.

3.1 The RAS

The RAS is an important regulator of cardiovascular homeostasis.(47) The RAS has been implicated in ECM remodelling,(36) and inflammatory pathways involved in AAA formation in animal models.(38, 47-49) The key peptide in the RAS is the octapeptide angiotensin II (Ang II), which is known to exert its proinflammatory effects by inducing the expression of several chemokines and adhesion molecules.(41, 50, 51) Continuous infusion of Ang II has been widely reported to result in AAA in the pro-atherosclerotic hyperlipidaemic apolipoprotein E deficient ($ApoE^{-/-}$) mouse.(48, 50, 52) In addition, a number of studies have implicated the RAS in human AAA pathogenesis.(53-56) The activities of the Ang II forming enzymes, angiotensin converting enzyme (ACE) and chymase have been reported to be upregulated in the aneurysmal aorta.(55, 56) Therefore, there has been a lot of interest in targeting the RAS pathway as a putative treatment for AAA. Consequently, ACE inhibitors and Ang II receptor blockers (ARB) have been investigated in several studies as putative pharmacological therapies for AAA. These drugs are already established as being beneficial in treating hypertension and heart failure.(57, 58)

Three ACE inhibitors (enalapril, captopril and Lisinopril) but not the angiotensin receptor blocker, losartan were reported to inhibit AAA development in the elastase infused rat model of AAA.(59) These medications were shown to attenuate aortic media elastin degradation independent of their effect on blood pressure and without diminishing the elastase-induced inflammatory response.(59) In contrast, Daugherty *et al.* demonstrated that losartan inhibited Ang II-induced AAA in $ApoE^{-/-}$ mice.(60) The discrepant effect of losartan on AAA formation suggests that ARBs exert different effects depending on the animal model. However, Fujiwara and colleagues reported that another ARB, valsartan inhibited AAA development in the elastase-induced AAA rat model independent of its antihypertensive effect.(61) *They showed that valsartan inhibited nuclear factor-κB (NF-κB) activation, macrophage infiltration, and MMP-2 and -9 expression.(61) Recently, employing the Ang*

II-induced ApoE$^{-/-}$ mouse model of AAA, we found that aliskiren, the direct renin inhibitor,(62) significantly inhibited AAA progression and reduced aortic arch atherosclerosis.(43) Aliskiren was also found to reduce aortic pro-renin receptor expression, mitogen-activated protein kinase activity, and aortic inflammation.(43)

Human studies are also contradictory. For example, in a population based case-control study, ACE inhibitor but not ARB prescription were reported to be significantly associated with a decreased risk of AAA rupture.(63) Contrary to this, Sweeting and colleagues reported an increased risk of aortic expansion in patients receiving ACE inhibitors in a prospective cohort study of patients enrolled in the UK small aneurysm trial.(64) Thus, there is conflicting evidence on the potential beneficial or detrimental effects of targeting the RAS for AAA therapy. There are a number of on-going clinical trials examining the effect of blocking the RAS on small AAA progression.(37) Examples of animal and human association studies linking the RAS with AAA are shown in Table 1.

3.2 Sex hormones

Until recently, it has been widely accepted that the female sex confers some form of protection from AAA.(65, 66) The predilection of AAA for the males and emerging data linking estrogen and estrogen receptor modulation with reduced inflammation in women,(67) has resulted in a number of studies investigating the effect of gonadal hormones on AAA pathogenesis *(Table 2).* For example, Ailawadi *et al.* reported that 17β-estradiol inhibited AAA development in an elastase rat model associated with decreased aortic medial macrophage infiltration, and lower MMP-9 concentrations.(68) Martin-McNulty and colleagues demonstrated a reduction in AAA size in mice receiving 17β-estradiol characterised by decreased expression of monocyte chemoattractant protein-1 (MCP-1), and NF-κB activity in the Ang II-infused mouse model of AAA.(69) In a separate study, Grigoryants *et al.* demonstrated that the selective estrogen receptor modulator, tamoxifen significantly reduced AAA, MMP-9 expression and inflammatory neutrophil infiltration in an elastase-induced AAA rat model.(70) This effect was partially abrogated by a catalase inhibitor suggesting that the superoxide pathway was involved. The effect of gonadal hormones on AAA development in animal models is not completely consistent. Henriques and colleagues reported that ovariectomy in female mice did not result in increased AAA formation whereas orchidectomy reduced aneurysm size in male mice in the Ang II-induced model of AAA.(71) Collectively, these data suggest that gonadal hormones may play a role in AAA formation; however more work is needed to clarify a safe and effective target for AAA therapy.

3.3 Inflammatory pathways

AAA is regarded as the consequence of a chronic inflammatory process due to the intense inflammation seen within AAA wall biopsies.(1, 44, 72, 73) A number of proinflammatory factors, such as reactive oxygen species (ROS), interleukin-6 (IL-6), MCP-1, and tumor necrosis factor-α (TNF-α) have been implicated in AAA pathogenesis.(74, 75) In addition, prostaglandins, a group of lipid autacoids derived from arachidonic acid and cyclooxygenase have been implicated in aortic

medial degradation through the production of MMPs.(76, 77) Evidence suggests that both prostaglandin E2 (PGE_2) and cyclooxygenase-2 (COX-2) are significantly upregulated in aneurysmal tissue and encourages VSMC apoptosis.(78-81) Consequently, medication designed to inhibit the inflammatory process has been studied as a means of deterring AAA expansion.

A number of studies examining the therapeutic potential of cyclooxygenase inhibitors in limiting AAA development have been described. For example, the selective COX-2 inhibitor celecoxib, a sulfonamide nonsteroidal anti-inflammatory drug (NSAID) was shown to decrease the incidence and severity of AAA in the Ang II-induced mouse model.(45) In addition, Gitlin *et al*. demonstrated that COX-2 deficient mice infused with Ang II failed to develop AAA.(82) These data suggest that COX-2 may serve as a putative pharmacotherapeutic target for AAA.

Indomethacin, another NSAID, have been demonstrated in two separate studies utilising an elastase-induced rat model of AAA to significantly inhibit PGE_2 and MMP-9 expression thereby maintaining elastin integrity and decreasing AAA expansion with no effect on the inflammatory infiltrate.(83, 84) Furthermore, Walton *et al*. demonstrated a significant reduction in AAA growth rate in patients receiving NSAIDs in a small case-control study involving 15 patients receiving NSAIDs and 63 patients without NSAIDs.(81) *Concerns regarding the safety of cyclooxygenase inhibitors particularly their association with increased incidence of major cardiovascular events including myocardial infarction and stroke,(85, 86) may deter further investigation of these agents as potential therapeutic targets for AAA.*

A number of agents modulating ROS production have been investigated including vitamin E (α-Tocopherol), a lipid-soluble antioxidant (reviewed in detail by Singh *et al*.).(87) Vitamin E is reported to inhibit the release of ROS, attenuate proinflammatory cytokine and chemokine release, and regress the expression of vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intercellular adhesion molecule-1 (ICAM-1). Vitamin E is also reported to inhibit cyclooxygenase expression by monocytes thereby abrogating PGE_2 synthesis.(87) It has been reported that vitamin E inhibits AAA formation in two different rodent models of AAA.(88, 89) Gavrila *et al*. reported reduced levels of ROS and aortic macrophage infiltration along with reduction in maximum AAA diameter and incidence of rupture in mice receiving vitamin E in a study employing the Ang II-induced mouse model of AAA.(89) Similarly, Nakahashi and colleagues reported that rats receiving vitamin E had significantly decreased AAA expansion rate compared to controls in the elastase-induced rat model of AAA.(88) *However, a randomised double-blind placebo-controlled trial by Tornwall et al. suggested that vitamin E and β-carotene supplements did not reduce the incidence of AAA diagnosis or rupture in patients.(90)*

A number of immune suppressants have been investigated as potential therapies for AAA. For example, rapamycin (sirolimus) an mTOR inhibitor used extensively in kidney transplants and in vascular stents to avert intimal hyperplasia,(91, 92) was shown to significantly reduce AAA development in the elastase-induced rat model of AAA via inhibition of MMP-9 and NF-κB

expression.(93) We also recently demonstrated that the rapamycin rapalog everolimus, restricts AAA development in the Ang II-induced ApoE$^{-/-}$ mouse model by suppressing the development and migration of bone marrow derived chemokine receptor 2 expressing monocytes.(44) *In vitro*, we found that everolimus abrogated Ang II-stimulated production of interferon gamma (IFN-γ) in ApoE$^{-/-}$ mice bone marrow. Furthermore, the potent immunosuppressive drugs, methylprednisolone and cyclosporine were demonstrated to inhibit AAA formation in an elastase-induced rat model of AAA.(94) The major difference between the cyclosporine treated and methylprednisolone treated groups was the presence of moderate oedema in the cyclosporine treated animals. However, both groups exhibited intact elastin lamellae.(94) Considering the generalised systemic effects of immune suppressants and the difficulty in achieving a balance between the beneficial and the detrimental effects of these medications, it is unclear whether this form of treatment would be appropriate for older patients at risk of cancer and serious infective complications.

Curcumin (diferuloylmethane), a natural phenol found in the dietary spice tumeric has been reported to exert anti-inflammatory effects via inhibition of the production of ROS and nitric oxide synthase enzymes.(95-97) Preliminary studies by Parodi *et al.* employing an elastase-induced mouse model of AAA revealed that curcumin decreased aortic tissue concentrations of MCP-1, IL-6, NF-κB, interleukin-1β (IL-1β) and MMP-9. AAA development in the mice that received oral administration of curcumin was reduced.(98) Given the potential carcinogenic effects ascribed to cucurmin,(99) caution is advised in furthering this agent as a potential therapy for AAA. *Examples of animal and human association studies investigating the therapeutic effect of targeting inflammatory pathways are outlined in Table 3.*

3.4 Cholesterol lowering agents

Statins are a class of lipid-lowering drugs, also known as 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors with putative beneficial pleiotropic effects including antioxidant, anti-inflammatory and anti-proteolytic effects which may be beneficial in various cardiovascular diseases.(100-104) Statins have also been shown to improve stability of atherosclerotic plaque, inhibit thrombogenesis, and improve endothelial function.(105, 106) Despite the lack of convincing association between serum cholesterol and AAA expansion rate, several data indicate that statin therapy may inhibit AAA pathogenesis due to the above-mentioned pleiotropic effects *(Table 4)*.(46, 107-113)

Simvastatin has been reported to inhibit AAA development in a number of rodent studies.(46, 107, 110, 114) For example, Steinmetz *et al.* demonstrated that simvastatin inhibited AAA formation independent of serum cholesterol levels in the C57BL/6 wildtype and in hyperlipidaemic ApoE$^{-/-}$ mice using the elastase-infused mice model of AAA.(107) The authors showed a reduction in MMP-9 expression with a marked increase in tissue inhibitor of metalloproteinase-1 (TIMP-1) expression, maintenance of elastin integrity, and VSMC preservation but no effect on inflammatory infiltrate

composition following administration of simvastatin.(107) In support, Kalyanasundaram *et al.* showed that simvastatin inhibited AAA formation in an elastase-induced rat model.(110) They also demonstrated that simvastatin reduced NF-κB and MMP-9 concentrations, and further downregulated the gene expression of several proinflammatory cytokines and chemokines.(110) In contrast, in a further study employing the Ang II-induced mouse model of AAA, there was no significant reduction in AAA diameter following simvastatin administration.(46) Interestingly simvastatin exerted a more potent effect on intimal atherosclerosis rather than on aortic dilation.(46)

Cerivastatin a synthetic statin withdrawn from the general circulation in 2001 (due to reports of fatal rhabdomyolysis),(115) has been reported to decrease MMP-9 concentration and neutrophil activation with no effect on TIMP-1 in *ex vivo* human AAA organ culture.(116) Furthermore, inhibition of cerivastatin activity abrogated these effects on proteolysis and inflammation.

Atorvastatin has been reported to prevent AAA development by suppressing macrophage recruitment via inhibition of MCP-1, MMP-12 and ICAM-1 but not MMP-9 expression in an elastase-induced rat model of AAA.(113) In a similar experiment, Houdek and colleagues did not find any significant reduction in AAA formation in mice administered atorvastatin.(117) They did report a noticeable improvement in elastin integrity and VSMC preservation in the atorvastatin treated group.(117) Takahashi *et al.*, demonstrated no significant effect of atorvastatin on aortic diameter in an Ang II-induced mouse model of AAA.(118) They did however show that combined therapy with amlodipine, a calcium channel blocker significantly suppressed aneurysm formation via inhibition of Rho-kinase activity and elastin degradation.(118) Also, we have previously reported that fenofibrate a peroxisome proliferator-activated receptor alpha (PPARα) activator used clinically to reduce triglycerides antagonizes Ang II-induced AAA in low-density lipoprotein receptor-deficient ($Ldlr^{-/-}$) and $ApoE^{-/-}$ mice.(48, 119)

Several human observational investigations report an association between statin treatment and reduced AAA progression.(108, 109, 111, 120-123) In a prospective study investigating the beneficial effect of simvastatin in 32 patients, Evans *et al.*, demonstrated a 40% reduction in MMP-9 levels in the AAA wall in patients randomised to simvastatin compared to placebo prior to open aneurysm repair.(111) Schweitzer and colleagues reported a reduction in MMP-13, transforming growth factor beta (TGF-β), but not MMP-9 in 19 patients administered atorvastatin compared to 19 patients not receiving atorvastatin.(124) Schouten *et al.* investigated the effect of statins on 150 patients under surveillance for AAA.(108) They demonstrated a significant reduction in AAA growth rate independent of other cardiovascular factors in 59 patients receiving statins compared to 91 patients not on statins, after approximately 3 years median follow-up.(108) In another retrospective study evaluating the effects of statins on the growth rate of small aneurysm in 211 patients, Karrowni and colleagues demonstrated a significant association between statins use and reduced AAA expansion.(122) They showed that the mean growth rate for 75 patients not receiving statins was 3.2 mm per year but 0.9 mm per year for 136 patients on statins.(122)

Some larger clinical studies, however have failed to confirm an association of statins with reduced AAA expansion rate.(125, 126) For example, in a multicentre large observational study analysing the effects of statins on AAA growth in 652 patients undergoing surveillance of small AAAs, we found no significant association of statins prescription with AAA growth.(126) Patients receiving statins (n=349) were compared with patients not prescribed statins (n=303). AAA growth were similar in both patient group,(126) which was in contrast to earlier but smaller studies described above.(108, 111, 122, 123) This finding was further reinforced by the Tromso study, in which Forsdahl *et al*. reported follow up of 4000 subjects over seven years.(127) They reported that the subjects receiving statins were more likely to develop AAAs. It is possible that statins prescription simply identified a sub-set of individuals with risk factors putting them at excess likelihood of developing an AAA, although the investigators did attempt to adjust for potential confounding factors.(127) A large number of studies have suggested improved perioperative and postoperative longer-term outcomes in patients prescribed statins prior to aneurysm repair.(101, 128-136) *Recent European and American guidelines suggest that patients with large AAAs being considered for intervention should receive statins because of considerable data linking statins with reduced cardiovascular events.(137, 138) A randomised trial to examine the benefit of statins in reducing AAA expansion would therefore be far more straightforward to undertake.*

3.5 NF-κB, Rho/Rho-kinase and c-Jun N-terminal kinase inhibitors

The pharmacological modulation of signalling pathways including c-Jun N-terminal kinase (JNK), NF-κB, Rho/Rho-kinase has been suggested as an effective therapy for AAA in rodent studies *(Table 5)*.(139-143) Wang *et al*. reported that Ang II-infused $ApoE^{-/-}$ mice given fasudil [5-(1,4-diazepane-1-sulfonyl) isoquinoline], a Rho-kinase inhibitor in their drinking water had both a reduced incidence and severity of Ang II-induced AAA. Fasudil was shown to reduce proteolysis by MMP-2 and MMP-9 with consequent decrease in VSMC apoptosis and AAA formation.(143)

In a different group of studies the therapeutic potential of JNK, an important regulator of activator protein 1 (AP-1, which is a key transcriptional regulator of MMP-9), has been described.(139, 141, 144) In calcium chloride-induced and Ang II-induced mouse models of AAA, Yoshimura *et al.* demonstrated that SP600125 (1,9-pyrazoloanthrone), a specific JNK inhibitor, completely abrogated the development of AAA by decreasing MMP-9 expression, macrophage infiltration and improving elastin integrity. SP600125 was also shown to reduce AAA size after experimental induction of AAA with improved elastin integrity by upregulating lysyl oxidase and prolyl-4-hydroxylase, enzymes critical for the crosslinking and stable maturation of elastin and collagen.(139) SP600125 was also shown to suppress the secretion of MMP-2 and MMP-9 in the walls of human AAA explants in culture.(141, 145)

A number of studies have suggested that medication-targeting NF-κB may be useful in treating AAA.(142, 143, 146, 147) NF-κB is a well-researched transcription factor that regulates numerous genes implicated in inflammation and immune response.(148-155) A number of proinflammatory cytokines (e.g TNF-α, IL-1, IL-6, IL-2), chemokines (e.g. IL-8),(148-150) adhesion molecules (e.g.

ICAM-1, VCAM-1), (151, 152) and proteolytic enzymes (e.g. MMPs, MMP-1, -2 and -3, -9),(153, 154) (155, 156) are directly regulated by NF-κB. NF-κB upregulation has been shown to promote experimental AAA in rats.(146) A recent study in an elastase-induced mouse model of AAA suggested that blocking NF-κB activity with pyrrolidine dithiocarbamate (PDTC) significantly reduced the incidence of AAA and AAA size via inhibition of IL-1β, IL-6 and MMP-9 expression.(142)

3.6 Protease inhibitors

AAA pathogenesis including formation, growth and eventual rupture is intricately linked with connective tissue destruction especially loss of aortic media and adventitia elastin.(157-161) Proteolytic enzymes such as MMP-9 and -2 have been implicated in ECM degradation resulting in aneurysm formation.(144, 162, 163) Animal based investigations,(164) as well as *in vitro* studies on human aortic tissue(157, 160) suggest that proteases including MMPs, cathepsins, and neutrophil elastase secreted by inflammatory cells and VSMC are involved in the destruction of the aortic wall and subsequent AAA formation.(157-160) MMPs are Zn^{2+} and Ca^{2+} dependent enzymes,(158, 165, 166) and are secreted in an inactive zymogen form.(157) They are then activated by mast cells and plasmin generated from plasminogen by the action of plasminogen activating factors such as urokinase-type plasminogen activator (uPA) and tissue plasminogen activator (tPA). Physiologically, MMP activity is strictly regulated by inhibitors such as α2-macroglobullins, α1-antitrypsin and TIMP, which help to control the connective tissue turnover rate. However, aberrant protease expression can result in unbalanced MMP activity, and lead to pathological destruction of the aortic media.(157, 167, 168) MMP-9 (gelatinase B), and MMP-12 (macrophage elastase) are elevated in animal models of AAA as well as plasma and sera from patients with AAA.(168, 169) MMP-3 (Stromelysin-1) and MMP-7 (matrilysin) are also reported to be increased in aneurysmal tissue.(160) Over expression of the collagenases MMP-1 (interstitial collagenase) and MMP-13 (collagenase 3) results in interstitial collagen degradation and promotes AAA formation. Additionally, high levels of MMP-2 (gelatinase A), are found in small AAAs, which suggests a role for MMP-2 in early aneurysm formation.(170)

The theory that *Chlamydia* or similar infections was important in AAA pathogenesis initially drove an interest in the use of antibiotics in the treatment of AAA.(171) Petrinec *et al.* initially reported that blocking the active form of MMP-2 and -9 with the tetracycline derivative, doxycycline suppressed AAA formation in an elastase-induced rat model of AAA.(172) Kaito and colleagues demonstrated in a similar model that doxycycline inhibited MMP-9 activity with consequent decrease in AAA development without affecting MMP-2 activity.(173) Accumulated evidence derived from *in vitro, in vivo* and human studies suggested that doxycycline preserved aortic elastin integrity in a dose dependent manner, reduced MMP-9 activity and AAA growth with no effect on MMP-14, -2 and TIMP expression.(157, 162, 173-182)

A study by Franklin *et al.* suggested that patients who received a bolus of tetracycline prior to elective aneurysm repair surgery had reduced MMP-9 and MCP-1 expression.(181) In another study,

preoperative administration of doxycycline was shown to decrease MMP-9 expression and increase abrogation of pro-MMP-2 activation in the aortic wall.(183) Mosorin *et al.* initially published a randomised placebo-controlled trial of doxycycline in 32 patients with small AAAs measuring between 30 and 55 mm.(184) They reported that doxycycline decreased AAA expansion rate in patients administered doxycycline compared to patients receiving placebo but the difference was not statistically significant.(184) In a double-blind randomised Phase II clinical trial of 36 patients with small AAAs, doxycycline was shown to be safe and well tolerated and associated with significant decrease in plasma MMP-9 levels with no significant effect on AAA expansion.(185) Linderman *et al*., reported that doxycycline reduced inflammation in AAA biopsies compared to placebo in a randomised trial of patients undergoing open AAA repair.(186) In a separate randomised trial in patients after endovascular AAA repair, Hackmann and colleagues found that doxycycline reduced plasma levels of MMP-9, which has been suggested as a biomarker of endograft failure.(187) Meijer *et al.* published the results of a large multicentre randomised, placebo-controlled, double-blind trial investigating the effect of doxycycline on 286 patients with small AAAs (mean aortic diameter ~43mm) completed in the Netherlands recently.(188) They reported that doxycycline administration was associated with increased AAA growth [4.1 mm, (n=144)] compared to the placebo allocated group [3.3 mm, (n=142)] after 18 months.(188) *Another doxycycline trial is currently ongoing in the USA. Other strategies of modifying aortic ECM remodeling are also been explored. For example, Allaire et al. demonstrated that overexpression of TIMP-1 in VSMC significantly reduced AAA development in a rat model of AAA.(72)* Despite encouraging data from pre-clinical studies, targeting ECM proteolysis has as yet not translated into a clinically useful strategy. *Examples of animal and human studies examining the effect of protease inhibitors on AAA are shown in Table 5.*

3.7 Immune cell modulators

A defining feature of AAA is inflammation including an extensive infiltration of mononuclear lymphocytes and macrophages in the AAA wall.(16, 17, 189) It is proposed that these cells release a cascade of cytokines that activate proteases and thereby degrade the vessel wall. The stimuli that initiate inflammation in human AAA still remain to be elucidated. Experimental evidence suggests that elastin and collagen degradation products in the aortic wall promote the recruitment of inflammatory cells.(17, 190, 191) The marked inflammation and the identification of IgG in AAA tissue which is reactive to ECM proteins supports the concept that AAA development is an autoimmune response.(192) A genetic investigation suggested an association between a human leukocyte antigen (HLA) allele and AAA (HLA-DQA1).(193) Both innate (natural killer/NK cells, mast cells) and adaptive (cytotoxic lymphocytes) immune effectors are elevated in the circulation of patients with AAA.(194-197) Helper T-cell type-1 (Th1) and type-2 (Th2) cytokines have been identified in both human AAA and animal models.(198) Proinflammatory molecules such as IL-6, IFN-γ, TNF-α, IL-8 and MCP-1 have been reported to be upregulated in AAA tissue and to be responsible for ECM remodelling.(17, 199, 200) Suppression of AAA development has been reported to be associated with the inhibition of inflammatory cells in rodent models.(196, 201, 202)

Mast cells have been implicated in AAA pathogenesis. They have been identified in human AAA biopsies, and mast cell deficient mice were shown to be resistant to experimental AAA.(196, 203) In both an elastase-induced and calcium chloride-induced mouse models of AAA, disodium cromoglycate (DSCG), a mast cell stabilizer was shown to significantly inhibit AAA growth by maintaining elastin architecture and decreasing inflammation whilst C48/80 a mast cell activator was shown to increase AAA growth.(196) The authors also demonstrated that mast cell deficient mice failed to develop elastase or calcium chloride induced AAA.(196) Similarly, Tsuruda *et al.* found that tranilast, a mast cell degranulation inhibitor attenuated AAA development in rodents.(202) There is considerable interest in employing mast cell stabilising agents as a therapy for patients with small aneurysms,(53) and a current randomised trial is examining this approach.

3.8 Anti-platelet therapy

Most AAAs contain intraluminal thrombus and we had previously reported a close correlation between thrombus volume and AAA diameter.(204) It has been demonstrated that AAA thrombus is a rich source of inflammatory cells, proteolytic enzymes and proinflammatory cytokines.(40, 73, 205) We have also demonstrated that circulating levels of thrombus products are significantly associated with AAA presence and progression in patients with small AAAs.(206, 207)

Platelet inhibition has been reported to inhibit AAA formation in rodent models.(205, 208) Tout *et al.* demonstrated that abciximab, a platelet aggregation inhibitor reduced both thrombus area and aneurysmal enlargement in a rat model of AAA.(205) In a similar study, another platelet aggregation inhibitor, ticagrelor (AZD6140) was shown to reduce elastin degradation and suppress AAA growth.(208)

Two association studies have suggested the efficacy of anti-platelet medication in limiting AAA progression.(209, 210) Karlsson and colleagues reported that the anti-platelet medication, aspirin (acetylsalicylic acid) was associated with reduced AAA expansion.(209) They also reported that a combination of aspirin and statins therapy was more powerfully associated with limited AAA expansion than aspirin or statins alone.(209) In a different study, Lindholt *et al.* reported that aspirin prescription was associated with reduced progression of small AAAs.(210) However, more recent and larger studies have failed to demonstrate any strong association between anti-platelet medication and AAA expansion.(64, 125, 126)

4. Conclusion and future directions

Animal and human data suggests that a complex group of mechanisms are involved in AAA pathogeneses. The last couple of decades have seen a massive increase in research assessing potential pharmacotherapy for AAA in experimental models. Several agents targeting mechanisms implicated in AAA pathogenesis including the RAS, proteolytic processes, inflammatory pathways, the immune

system and intracellular signalling pathways, have been reported to be effective in pre-clinical studies. It should be noted that the therapeutic manipulation of microRNAs and their target genes have also been shown to limit experimental AAA progression recently.(211, 212) However, the efficacy of these agents has not currently been confirmed in large clinical trials. For example, the efficacy of the very promising tetracycline derivative, doxycycline reported to inhibit AAA progression in many rodent pre-clinical and clinical studies, has recently come into doubt with the report of no benefit in a large randomised clinical trial.(188) *The difficulty in translating results from animal studies to patients is likely due to a number of factors. Firstly investigating drug therapy targets in patients with AAA is complex. These patients are mainly older adults that frequently have co-morbidities, including coronary heart disease and cancer, precluding the use of medications that may have significant toxic side effects. Given the co-morbidities of AAA patients, they are often receiving a range of medications for other indications, which also makes it difficult to effectively test some medications in trials such as statins, which are already indicated for cardiovascular risk reduction. Secondly the current major animal models of AAA rely on acute injury to the aortic wall and it remains unclear how well these models are suited to identifying treatment targets for human AAA. Thirdly the development of targeted drugs for any medical condition can take a prolonged time and requires significant investment particularly from pharmaceutical companies. Only recently have drug companies become interested in this area and therefore a lag in the development of medications is expected. It is also possible due to the multifactorial nature of AAA that a successful drug will have to target multiple pathways. There are a growing number of trials of medications in AAA patients and therefore it is expected that one or more effective medications will be identified in the near future. It is possible that better delivery of therapeutic agents,(213-215) and a means of monitoring the efficiency of these agents on AAA progression in blood (e.g. using biomarkers),(216) may help identify effective medications for AAA patients.* Whether the use of animal models is an effective means to identify appropriate agents to limit AAA progression remains to be proven.

List of abbreviations

Abdominal aortic aneurysm (AAA), extracellular matrix (ECM), matrix metalloproteinases (MMPs), vascular smooth muscles (VSMC), Intraluminal thrombus (ILT), Neutrophil gelatinase associated lipocalin (NGAL), renin angiotensin system (RAS), angiotensin II (Ang II), angiotensin converting enzyme (ACE), Ang II receptor blockers (ARB), apolipoprotein E deficient ($ApoE^{-/-}$), nuclear factor-κB (NF-κB), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), reactive oxygen species (ROS), interleukin-6 (IL-6), prostaglandin E2 (PGE_2), cyclooxygenase e.g cyclooxygenase-2 (COX-2), nonsteroidal anti-inflammatory drug (NSAID), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), interferon gamma (IFN-γ, interleukin-1β (IL-1β), 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA), tissue inhibitor of metalloproteinase-1 (TIMP-1, c-Jun N-terminal kinase (JNK), peroxisome proliferator-activated receptor alpha (PPARα), transforming growth factor beta (TGF-β), pyrollidine dithiocarbamate (PDTC), human leukocyte antigen (HLA), urokinase-type plasminogen activator (uPA), tissue plasminogen activator (tPA), helper T-cell (Th), and disodium cromoglycate (DSCG).

Conflict of interest

None Declared

Funding

Research undertaken by J.G is supported by the National Health and Medical Research Council (project grant numbers 1063476, 1022752, 1021416, 1020955, 1003707; Practitioner Fellowship number 1019921; and a Centre of Research Excellence number 1000967), the Queensland Government and The Townsville Hospital Private Practice Trust Fund. SWS is supported by the National Heart Foundation (NHF) of Australia Fellowship (PF12B6825). The funding bodies played no role in the production of this paper.

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Figure Legend

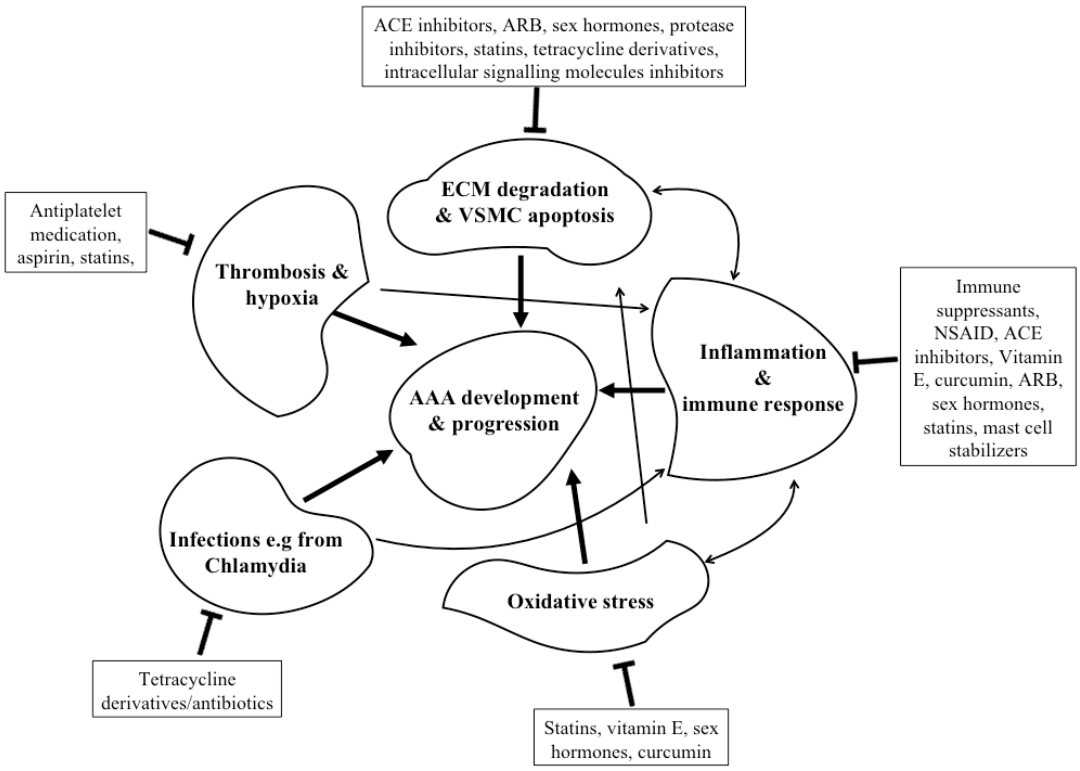

Figure 1. Current pharmacotherapeutic strategies/agents of relevance for abdominal aortic aneurysm (AAA) treatment. The flow chart shows key processes involved in AAA pathogenesis and potential therapeutic targets to deter AAA development and progression. ECM= extracellular matrix, VSMC= vascular smooth muscle cells, NSAID= non-steroidal anti-inflammatory drugs, ARB= angiotensin II receptor blocker

Tables

Table 1 Examples of studies assessing the effect of modulating the renin-angiotensin system on AAA development, progression and rupture

Type of Study	Agent/Medication	Design	Effect on AAA
Animal	Enalapril, captopril and lisinopril	Elastase/rat(59)	Decreased development
	Losartan	Ang II/ ApoE$^{-/-}$ /mice(60)	Decreased development
	Valsartan	Elastase/rat(61)	Decreased development
	Aliskiren	Ang II/ ApoE$^{-/-}$ /mice(43)	Decreased progression
Human	ACEi	Case-control(63)	Decreased rupture
	ACEi	Cohort(64)	Increased risk of progression

ACEi= angiotensin converting enzyme inhibitor; Ang II= angiotensin II; ApoE$^{-/-}$= apolipoprotein E deficient

Table 2 Examples of animal studies examining the effect modulating sex hormones on AAA development and severity

Type of Study	Agent/Medication	Design	Effect on AAA
Animal	17β-estradiol	Elastase/rat(68)	Decreased development
	17β-estradiol	Ang II/ $ApoE^{-/-}$ /mice(69)	Decreased size
	Tamoxifen	Elastase/rat(70)	Decreased development
	Ovariectomy	Ang II/ $ApoE^{-/-}$ /mice(71)	No effect
	Orchidectomy	Ang II/ $ApoE^{-/-}$ /mice(71)	Decreased development

Ang II= angiotensin II; $ApoE^{-/-}$= apolipoprotein E deficient

Table 3 Examples of studies assessing the effect of targeting inflammatory pathways on AAA development and progression

Type of Study	Agent/Medication	Design	Effect on AAA
Animal	Celecoxib	Ang II/ ApoE$^{-/-}$ /mice(45)	Decreased development and severity
	COX-2 deficiency	Ang II/COX-2$^{-/-}$ /mice(82)	Decreased development
	Indomethacin	Elastase/rat(83, 84)	Decreased progression and risk of rupture
	Vitamin E	Ang II/ ApoE$^{-/-}$ /mice(89)	Decreased progression and rupture
		Elastase/rat(88)	Decreased progression
	Curcumin	Elastase/mice(98)	Decrease development
	Rapamycin	Elastase/rat(93)	Decreased progression
	Everolimus	Ang II/ ApoE$^{-/-}$ /mice(44)	Decreased development
	Methylprednisolone and cyclosporine	Elastase/rat(94)	Decreased development
Human	NSAID	Case-control(81)	Decreased progression
	Vitamin E and β-Carotene	RCT(90)	No effect on progression

Ang II= angiotensin II; ApoE$^{-/-}$= apolipoprotein E deficient: COX-2$^{-/-}$= cyclooxygenase 2 deficient; RCT= randomised control trial

Table 4 Examples of studies assessing the effect of cholesterol lowering agents on AAA development and progression

Type of Study	Agent/Medication	Design	Effect on AAA
Animal	Simvastatin	Ang II/ ApoE$^{-/-}$ and Ang II/C57Bl6/mice(107)	Decreased AAA development
		Ang II/ ApoE$^{-/-}$ and Ang II/LDLR$^{-/-}$/mice(46)	Limited effect
		Elastase/rat(110)	Decreased progression
	Atorvastatin	Elastase/rat(113)	Decreased progression
		Elastase/rat(117)	Limited effect on progression
		Ang II/ ApoE$^{-/-}$ /mice(118)	No effect
	Atorvastatin + amlodipine	Ang II/ ApoE$^{-/-}$ /mice(118)	Decreased development
	Fenofibrate	Ang II/ ApoE$^{-/-}$ /mice(48)	Decreased progression
		Ang II/ LDLR$^{-/-}$ /mice(119)	Decreased progression
Human	Statin	Retrospective(108)	Decreased progression
		Retrospective(122)	Decreased progression
		Cohort(126)	No effect
		Prospective(127)	Potentially increased development

Ang II= angiotensin II; ApoE$^{-/-}$= apolipoprotein E deficient: C57Bl6= C57 black 6; LDLR$^{-/-}$= low density lipoprotein receptor deficient

Table 5 Examples of studies assessing the effect of targeting signalling pathways and proteases on AAA development and progression

Type of Study	Agent/Medication	Design	Effect on AAA
Animal	Fasudil	Ang II/ ApoE$^{-/-}$ /mice(143)	Decreased development and severity
	1,9-pyraloanthrone (SP600125)	Ang II/ ApoE$^{-/-}$ /mice and CaCl2/mice(139)	Decreased development
	Pyrrolidine dithiocarbamate (PDTC)	Elastase/rat(142)	Decreased development and size
Animal	Doxycycline	Elastase/rat(172)	Decreased development
		Elastase/rat(173)	Decreased progression
Human	Doxycycline	Prospective	Limited effect on progression
		Pilot(184)	Decreased progression
		RCT(188)	Possibly increased progression

Ang II= angiotensin II; ApoE$^{-/-}$= apolipoprotein E deficient: CaCl2= calcium chloride; RCT= randomised control trial