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Review Article

Novel pharmacological approaches in abdominal aortic aneurysm

Lídia Puertas-Umbert[1,2,*], Rafael Almendra-Pegueros[1,*], Francesc Jiménez-Altayó[3,4], Marc Sirvent[2,5], María Galán[1,2,6], José Martínez-González[1,2,7] and Cristina Rodríguez[1,2]

[1]Institut d'Investigació Biomèdica Sant Pau (IIB SANT PAU), Barcelona, Spain; [2]CIBER de Enfermedades Cardiovasculares, ISCIII, Madrid, Spain; [3]Department of Pharmacology, Therapeutics and Toxicology, School of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain; [4]Neuroscience Institute, Universitat Autònoma de Barcelona, Barcelona, Spain; [5]Departamento de Angiología y Cirugía Vascular del Hospital Universitari General de Granollers, Granollers, Barcelona, Spain; [6]Departamento de Ciencias Básicas de la Salud, Universidad Rey Juan Carlos, Alcorcón, Spain; [7]Instituto de Investigaciones Biomédicas de Barcelona (IIBB-CSIC), Barcelona, Spain

Correspondence: José Martínez-González (jose.martinez@iibb.csic.es) or Cristina Rodríguez (crodriguezs@santpau.cat)

Abdominal aortic aneurysm (AAA) is a severe vascular disease and a major public health issue with an unmet medical need for therapy. This disease is featured by a progressive dilation of the abdominal aorta, boosted by atherosclerosis, ageing, and smoking as major risk factors. Aneurysm growth increases the risk of aortic rupture, a life-threatening emergency with high mortality rates. Despite the increasing progress in our knowledge about the etiopathology of AAA, an effective pharmacological treatment against this disorder remains elusive and surgical repair is still the unique available therapeutic approach for high-risk patients. Meanwhile, there is no medical alternative for patients with small aneurysms but close surveillance. Clinical trials assessing the efficacy of antihypertensive agents, statins, doxycycline, or anti-platelet drugs, among others, failed to demonstrate a clear benefit limiting AAA growth, while data from ongoing clinical trials addressing the benefit of metformin on aneurysm progression are eagerly awaited. Recent preclinical studies have postulated new therapeutic targets and pharmacological strategies paving the way for the implementation of future clinical studies exploring these novel therapeutic strategies. This review summarises some of the most relevant clinical and preclinical studies in search of new therapeutic approaches for AAA.

Introduction

Abdominal aortic aneurysm (AAA) is a progressive and life-threatening vascular degenerative disease affecting between 4% and 8% of men aged >65 years [1,2]. AAA consists in a focal dilation of the abdominal aorta exceeding 50% of its normal diameter (or >3 cm). AAA progresses insidiously, increasing the risk of aortic rupture, the more severe complication of this disease and a public health concern that often results in sudden death and accounts for 150,000–200,000 deaths each year globally.

Aneurysm growth is boosted by ageing, atherosclerosis and further by smoking, the major modifiable risk factor recognised for this disease. In the last two decades and specific countries, decreased prevalence and mortality from ruptured AAA have been attributed to the significant decline in smoking rates [2,3]. Additionally, the male sex is a major predisposing factor for this disease that exhibits a prominent sexual dimorphism. Indeed, AAA prevalence is 4-6 times higher in men than in women, although, the risk of aneurysm rupture is greater in women who also have worse outcomes after surgical repair. Notably, genetics is behind AAA aetiology with a double risk of aneurysm development in individuals with a family history of AAA in a first-degree relative [2,3].

The pathophysiology of AAA is complex and involves several interconnected and mutually regulated processes. Clues provided by human aneurysmal specimens corresponding to end-stage phases of the disease or by preclinical models indicate that AAA is a chronic inflammatory disease associated with the local

*These authors contributed equally to this work.

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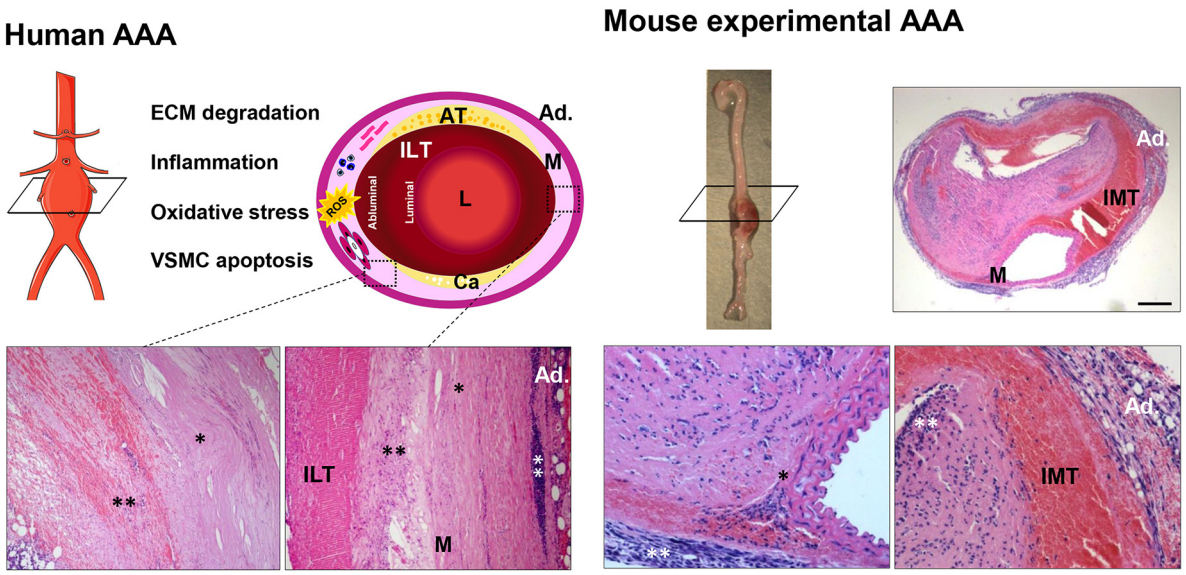

Figure 1. Pathophysiology of abdominal aortic aneurysm (AAA)

The scheme depicts the pathophysiological characteristics of human AAA, shows the main mechanisms involved in its development and evidences the common aspects, but also the differences between human and murine aneurysmal lesions. Human AAA is featured by an important inflammatory infiltrate that produces proteases, responsible for ECM (extracellular matrix) degradation, and releases cytokines and Reactive Oxygen Species (ROS) leading to the loss of VSMC due to apoptosis and necroptosis These processes favour the weakening of the arterial wall and elastin degradation. Commonly, a non-occlusive and multilayered intraluminal thrombus (ILT) covers the human aneurysmal sac, allowing blood to flow through a preserved lumen (L) and providing an additional source of ROS and proteolytic mediators. AAA often coexist with atherosclerosis (AT) and calcium deposits (Ca). The images below correspond to aortic sections from patients subjected to surgical repair. (*) Denote areas devoid of VSMC with a disorganised ECM, while (**) indicate areas enriched in inflammatory cells. Panel on the right side show an aneurysmal lesion from angiotensin II-infused ApoE$^{-/-}$ mice that, in conjunction with aneurysms induced by $CaCl_2$ or elastase perfusion, well-established models of AAA, are only partially representative of the human disease. In the angiotensin II-infused ApoE$^{-/-}$ model, aneurysms show a suprarenal location with an intramural thrombus (IMT), but similar to human lesions, vascular inflammation, and ECM remodelling feature experimental AAA. Ad: Adventitia; M: media. The figure was partly generated using Servier Medical Art provided by Servier, licenced under a Creative Commons Attribution 3.0 unported license.

upregulation of proteinases, responsible for the progressive destruction of the structural components of the vascular wall, elevated production of reactive oxygen species (ROS), and depletion of medial vascular smooth muscle cells (VSMC) (Figure 1) [2]. However, although these are the main mechanisms driving this chronic degenerative disease and considerable progress has been made in this field, a deep understanding of the intricate pathways involved in aneurysm progression and rupture is still lacking, which has hampered the development of effective pharmacological interventions for the treatment of AAA.

Certainly, despite AAA remains a major public health issue, there is a lack of pharmacological therapies limiting AAA progression, and surgical repair, by either open surgery or endovascular repair (EVAR), is the only therapeutic option. This intervention is exclusively indicated for asymptomatic patients at a high risk of aortic rupture or symptomatic or ruptured aneurysms, being aortic diameter the most reliable marker to assess aneurysm rupture risk. Specifically, surgical repair is recommended for male patients with AAA diameters equal to or larger than 5.5 cm or for women in whom aortic diameter reaches at least 5 cm. Unfortunately, clinical trials reported no benefit of surgical repair for AAA measuring less than 5.5 cm [3–7] and therefore, no therapeutic options are available for patients with small and asymptomatic aneurysms, who must be subjected to conservative management consisting of close monitoring with no other alternative. This follow-up involves imaging surveillance of disease progression until the aortic diameter reaches the surgical threshold size when the risk of rupture exceeds surgical risk [8]. The absence of medical therapies that halt or slow down AAA progression has encouraged an active search for identifying new

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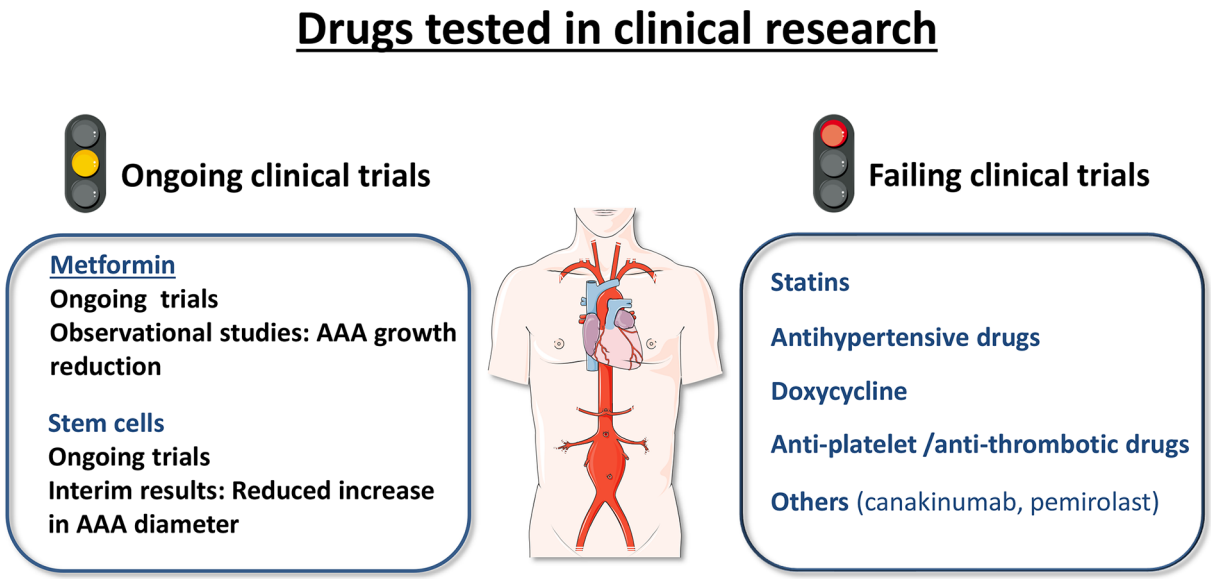

Figure 2. Clinical trials evaluating pharmacological interventions in abdominal aortic aneurysm (AAA)

Ongoing clinical trials are assessing the interest of metformin and stem cells as candidate therapeutic strategies for AAA. Clinical trials analysing the effectiveness of statins, antihypertensive drugs, doxycycline, anti-platelet and anti-thrombotic therapies and other drugs with anti-inflammatory activity failed to evidence a benefit on AAA progression. The figure was partly generated using Servier Medical Art provided by Servier, licenced under a Creative Commons Attribution 3.0 unported license.

therapeutic targets. In this context, several randomised clinical trials have evaluated the efficacy of different therapeutic approaches for the management of this disease, including statins, doxycycline, and anti-hypertensive drugs, among others; however, none of them has convincingly demonstrated a clear benefit on aneurysm expansion. This article provides an overview of previous and ongoing clinical trials in AAA and critically reviews current progress in preclinical research aiming at discovering novel candidate compounds or repurposing strategies for pharmacological intervention in this disease.

Clinical trials for testing pharmacotherapies limiting AAA progression

None of the tested drugs against AAA has conclusively evidenced a benefit on aneurysm progression or rupture, as summarised below (Figure 2). Major shortcomings that could underlie the failure of clinical trials evaluating pharmacological interventions in AAA might be related to the small cohort size and short follow-up, as well as the lack of reliable methods for determining aneurysm diameter, as discussed below.

Statins

Beyond the lipid-lowering activity of statins, it is now well recognised that some of their beneficial responses are derived from their pleiotropic effects, such as the improvement of endothelial function, the reduction of inflammation and oxidative stress and the attenuation of thrombosis [9–11]. Thus, several researchers have hypothesised that statins might limit AAA development through their anti-inflammatory and antioxidant properties, further supported by preclinical data in animal models [12]. Accordingly, two different studies addressing the impact of short-term preoperative treatment with statins in patients undergoing elective open repair for AAA revealed that this pharmacological intervention decreased vascular MMP9 levels [13], and inflammation, although did not significantly affect the progression of AAA [14]. Subsequently, several observational studies have evaluated the use of statins in the management of AAA, showing inconsistent data. Half of them argued in favour of a lower aneurysm growth rate in patients on statin therapy, while others, specifically the largest and most robust trials, reported no significant benefit on AAA progression [15]. Similarly, systematic reviews and meta-analyses of observational studies assessing the effect of statin therapy on growth outcomes led to discordant conclusions [16–18]. Consequently, the use of statins as a pharmacological approach to halt AAA growth remains uncertain. However, evidence that statins reduce long- and short-term mortality in patients after surgical AAA repair improving all-cause survival [16,19,20] sustains the

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prescription of statins for the management of this disease, in agreement with current guidelines. Prospective, and multicentre rigorous trials would be needed to clarify whether statins could limit aneurysm progression.

Antihypertensive drugs

Although preclinical studies reported convincing data about the effectiveness of antihypertensive drugs to ameliorate AAA formation [21–28], conclusive evidence supporting their clinical application is still lacking. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers (ARB), and propranolol were the hypotensive agents more extensively studied. Two multicentre randomised trials tested the effectiveness of propranolol in limiting aneurysm growth. However, both of them reported no significant benefit of this drug on aneurysm expansion, while the low compliance with the treatment in the groups of propranolol-treated participants compromises the significance of these studies [29,30]. Likewise, the pharmacological manipulation of the renin–angiotensin system (RAS) by using ARBs has been proposed as a therapeutic option in patients with AAA, boosted by the benefit provided by this strategy in murine models of AAA [24–28]. Unfortunately, the first randomised, double-blind, placebo-controlled trial assessing the efficacy of telmisartan to slow the growth of small AAA (TEDY trial) has failed to demonstrate a benefit of this drug on aneurysm progression after 2 years of follow-up [31]. Interestingly, recent additional analysis in a subset of patients enrolled in this trial has revealed that telmisartan decreases peak wall stress (PWS) and peak wall rupture index (PWRI) in individuals with small AAA, arguing in favour of additional extended and more powered studies addressing this target [32]. Because of the essential role of Ang II signalling in AAA, special mention deserves the recently reported attenuation of experimental AAA by angiotensin-(1-7) [33], which is related to the stimulation of Mas and AT2 receptors, in agreement with previous studies in murine models supporting the benefit of AT2 agonism on aneurysm progression [34]; these data lay the foundations of future trials addressing the usefulness of AT2 agonists for this disorder. Finally, regarding ACE inhibitors it should be noted that the encouraging conclusions raised from a population-based case–control study reporting that ACE inhibition is related to a reduced risk of AAA rupture [35], were subsequently dismissed based on data from three independent trials [36–38], one of them even reporting a faster AAA growth in patients taking ACE inhibitors [37].

Targeting ECM remodelling: doxycycline

Doxycycline has become the pharmacological candidate for the treatment of AAA most extensively studied from the 90s, in both preclinical and clinical settings. Doxycycline is a tetracycline that besides its antibiotic activity behaves as a MMP inhibitor at sub-antimicrobial dose. This property aroused the interest of the scientific community in doxycycline and its relevance for the treatment of diseases in which enhanced MMP activity plays a critical pathophysiological role, such as AAA [39]. The earliest preclinical studies reported the ability of doxycycline to reduce the incidence of AAA, preserving elastin integrity and attenuating gelatinolytic activity in different animal models [40–43]. These data fostered the development of the first clinical trials, conducted in a limited number of patients, but evidencing that a short-term doxycycline treatment prior to elective AAA repair suppressed aortic MMP expression and activity [44,45] and attenuated vascular inflammation [46]. Interestingly, no benefit on the progression of already established AAA was found in animal studies [47] and this notion could be also extended to humans. In fact, a pilot trial in patients receiving doxycycline for three months evidenced no differences in aneurysm size or the rate of aneurysm growth after 18 months of surveillance [48], while results from a placebo-controlled randomised clinical trial published in 2013 even suggested that doxycycline aggravates aneurysm growth [49]. Concerns about the use of a dose too low to be effective have been raised in this last study, in which a significant number of treated patients had to be excluded from the final analysis [49]. Recently, the N-TA^{3}CTrial that enrolled 254 patients with small infrarenal aneurysms tried to shed more light on this matter. This trial concluded that a 2-year doxycycline treatment does not attenuate the growth of AAA [50] consistent with a previous 6-month study conducted by the same researchers [51]. Of note, the AAA growth rate found in the N-TA^{3}CTrial was lower than that initially expected, suggesting that a longer follow-up would have been necessary to appreciate any benefit. Although being disappointing, a reduction in serum C-reactive levels has been repeatedly found in this and previous trials [48,50] and therefore a favourable response to doxycycline in AAA patients could not be totally ruled out, warranting further research.

Anti-platelet and anti-thrombotic therapy

The presence of a non-occlusive intraluminal thrombus (ILT) covering the aneurysmal sac is a common feature in 70–80% of patients with AAA. The ILT seems to play a critical role in disease progression. Certainly, it is a biologically active and dynamic entity that entraps a myriad of cellular elements including erythrocytes, platelets, neutrophils, and macrophages, producing proteases, cytokines and ROS that favour the weakening of the arterial wall

and promoting local hypoxia. This scenario has substantiated the potential of anti-thrombotic/anti-platelet therapies in the fight against AAA, supported by preclinical studies in animal models evidencing that this strategy limits aortic rupture or reduces aortic diameter [52–54]. However, although some studies showed that antiplatelet therapy with aspirin slows aneurysm growth in patients with middle-sized AAA [55], other clinical trials show inconsistent data [56,57], including a recent randomised clinical trial with the platelet inhibitor ticagrelor, which found no benefit on aneurysm growth in patients with small AAA [58]. Similarly, a retrospective analysis reported no benefit on patient outcomes with this strategy [59], while a recent systematic review and meta-analysis concludes that there is a lack of high-quality data to sustain the clinical benefit of antithrombotic therapy in patients with AAA [60]. Further, concerns have been raised about both the increased bleeding risk related to this therapy in the event of aneurysm rupture [56] and the association of long-term anticoagulation with type II endoleaks in patients subjected to EVAR [61,62], thus supporting that anticoagulation should be reconsidered. Novel well-designed and large clinical trials and more in-depth knowledge about the impact of ILT on individual biomechanics and aneurysm growth will be needed to draw clear conclusions.

Metformin

Diabetes is a major risk factor for cardiovascular diseases. Despite atherosclerosis and AAA sharing many of their risk factors [63], a paradoxical protective role of diabetes on the incidence, prevalence, growth rate and rupture of AAA has been repeatedly noticed in several study populations and meta-analysis [64–69]. The benefit associated with diabetes is gender-specific, exclusively circumscribed to males, while no difference in AAA incidence between diabetic and non-diabetic females has been detected [64]. These data raised the suspicion that the strong negative association between diabetes and AAA could rely on the medication used for the management of these patients, being metformin one of the most prescribed anti-diabetic drugs. Since then, it has become evident that metformin prescription is consistently associated with a significant reduction in aneurysm growth [70], but also in the need of AAA repair or aortic rupture-related deaths (Table 1) [70–77]. Besides its glucose-lowering properties, positive vascular effects have been attributed to metformin, including, the attenuation of vascular inflammation, ROS production and neovascularization and the regulation of transduction pathways critical for AAA development such as AMP-activated protein kinase (AMPK) [78–81], mechanisms that could underlie the protection against AAA rendered by metformin. It should be noted, however, that although cohort studies and case-control studies support the ability of metformin to ameliorate AAA progression and aneurysm-related events, randomised controlled trials are needed to state this assumption more clearly. In the most recent years three trials have been launched addressing this issue: (i) the limiting AAA with metformin (LIMIT) trial (NCT04500756), (ii) the metformin therapy in non-diabetic AAA patients (MetAAA) trial (NCT03507413) and (iii) the abdominal aortic aneurysm growth inhibition (MAAAGI) trial (NCT04224051). These ongoing trials will bring new more rigorous evidence sustaining the favourable outcome afforded by metformin in AAA and its repurposing, which could provide a safe and cost-effective therapeutic strategy for this disorder.

Stem cells

Cell-based therapies have become a promising approach for cardiovascular disorders. Due to the regenerative properties of stem cells, cellular therapies have gained growing attention for instance, for patients with myocardial infarction or critical limb ischemia, but also preclinical data suggest their interest as a therapeutic option in AAA. Several cell types have been assessed in murine models of AAA, being mesenchymal stem cells (MSCs) the most extensively studied. However, dissimilar sources, doses and routes of administration have been assessed, which does not allow us to draw more clear conclusions [82]. Of note adipose-tissue derived MSCs from patients with AAA exhibit enhanced senescence [83], while safety issues regarding the risk of oncogenic transformation should be solved; thus a deep understanding of MSCs biology is urgently needed before considering MSCs-based therapeutic strategies.

A huge number of studies found that MSCs induce a vascular reparative response that leads to an attenuation of AAA development in murine models [82,84–87]. This effect seems to rely on paracrine responses mediated by the production of anti-inflammatory cytokines [85], the secretion of extracellular vesicles with paracrine immunomodulatory features [86], and the preservation of VSMC contractile phenotype [87]. Although an important number of these investigations reported the engraftment of MSCs into the arterial wall [85,88,89], evidence about their differentiation into VSMC or endothelial cells is limited [89], further supporting that paracrine-mediated effects underlie their benefit. Unfortunately, clinical trials assessing the benefit of MSCs-based therapies in AAA are scarce. The VIVAAA trial (NCT02846883) aiming to explore the safety and effectiveness of allogeneic MSCs in decreasing inflammation and aneurysm growth was prematurely interrupted due to slow enrolment and no results have been posted. In turn, the design of ARREST, a phase I, randomised controlled trial analysing the impact of MSCs infusion on aortic diameter and inflammatory parameters in patients with small AAA was initiated in 2018. Interim results in a small group of

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Table 1 Cohort studies on metformin in patients with AAA

Ref.	AAA patient characteristics	Male sex (%)	Average follow-up (years)	Diabetics (%)	Metformin prescription (%)	Outcome	Difference between using and not using metformin
[77]	Diabetics/untreated AAA (*n*=58) Age, years: 72.0 (1.0)§	82.7	2.6	100	25.8	Maximum aortic diameter growth	−1.30 (–1.64, −0.96) ‡
[75]	**Cohort 1** Patients with AAA (*n*=1357) Age, years: 73.9 (6.3)§	89.9	3.6	15.9	8.6	Maximum aortic diameter growth	−0.59 (–1.09, −0.09)‡
	Cohort 2 Patients with AAA (*n*=287) Age, years: 72.6 (7.6)§	81.8	2.9	24.0	13.5	Maximum aortic diameter growth	–1.15 (−2.16, –0.14)‡
	Cohort 3 Patients with AAA (*n*=53) Age, years: 73.1 (7.4)§	84.9	1	35.8	30.1	Maximum aortic diameter growth	−1.09 (–1.89, −0.29)‡
[78]	Diabetics/unruptured AAA (*n*=13,843) Age at AAA diagnosis, years: 69.8 (7.8)§	99.4	4.2	100	39.7	Maximum aortic diameters growth	–0.30 (−0.37, –0.23)‡
[79]	**Cohort 1** Asymptomatic/unrepaired AAA (*n*=1080) Age, years: 73.4 (7.2)§	81.5	3.2	21.6	11.9	Incidence of AAA repair or death due to aneurysm rupture AND maximum aortic diameter growth	0.46 (0.26, 0.80)¤ –0.52 (−0.97, −0.07)‡
	Cohort 2 Asymptomatic/unrepaired AAA (Ø ≤50 mm; *n*=763) Age, years: 73.5(7.3)§	79.8	3.6	76.2	13.8		0.45 (0.21, 0.96)¤ −0.68 (–1.37, 0.01)‡
[81]	**Cohort 1** – Diabetes/no metformin (*n*=43.073) Age, years: 72.27 (7.85)§ **Cohort 2** – Diabetes/metformin (*n*=24.361) Age, years: 69.65 (7.15)§	100	5	Cohort 1 and 2 100	36.1	Surgery and/or death after AAA diagnosis	Cohort 1 0.88 (0.85, 0.91)¤ Cohort 2 0.93 (0.84, 1.04)¤
[80]	Baseline Ø ≥30mm (n = 526) Age, years: 69.0 (5.7)§	94.2	3.2	18.6	12.3	Maximum aortic diameter	−0.50 (–1.05, 0.05)‡
[76]	Patients undergoing AAA repair (n = 306) Age, years: 71.6 (5.8)§	NM	0.1	25.2	17.6	Maximum aortic diameter growth	0.09 (0.02, 0.47)‡

Ø: Aortic diameter; §: Mean (standard error);‡: Mean difference, 95% IC; ¤:Odds ratio, 95% IC; NM: Not mentioned.
Adapted from [82].

patients evidenced that MSCs infusion induces regulatory T cells (Tregs; 14 days post-infusion) and, after a 12-month follow-up, suppresses AAA inflammation (determined by 18-fluorodeoxyglucose uptake) associated with a reduced increase in aortic diameter [90]. Although the sample size was too small for statistical analysis, these promising results pave the way for larger trials exploring this novel therapeutic strategy in AAA, while data after the scheduled 5-year follow-up are eagerly awaited.

Other clinical trials

The inflammatory response is critical for the pathogenesis of AAA and mast cells are important players in the progression of this disorder. Mast cells release a large number of eicosanoids, cytokines and chemokines, which activate the renin–angiotensin system, contribute to neovascularization and VSMC apoptosis and promote the activation and release of proteolytic enzymes responsible for aortic wall weakening [91]. While compelling evidence supports the contribution of mast cells to experimental AAA [92,93] and a positive correlation between aortic diameter and the number of infiltrated mast cells has been detected in human aneurysmal samples [94], the AORTA trial, analysing the benefit provided by the mast cell inhibitor pemirolast, reported no significant impact on the growth of medium-sized AAAs [95]. Similarly, the study launched by Novartis focused on the anti-IL-1β antibody canakinumab in subjects with AAA showed a lack of efficacy in modifying aneurysmal size and was prematurely finished because the study

Table 2 Drugs against AAA tested in clinical trials

Drugs	Evidence from preclinical studies	Evidence from clinical studies	New clinical trials
Statins	Might limit AAA development through its anti-inflammatory and antioxidant properties [12].	Decrease in vascular MMP9 [13]. Inconsistent data regarding AAA progression [16–18]. Statins improve survival after AAA repair [16,19,20].	Prospective and multicentre rigorous trials are needed to clarify the impact of statins on AAA growth.
Antihypertensive drugs	Antihypertensive drugs ameliorate AAA formation [21–28].	Propranolol, telmisartan and ACEi failed to reduce AAA formation and growth [29,30]. Risk of faster AAA growth with ACEi [37].	Prospective trials in patients with small AAA will be required in view of reduced PWS and PWRI.
Doxycycline	Reduction of incidence of AAA, preserving elastin integrity and attenuating gelatinolytic activity [40–43].	Doxycycline suppressed aortic expression of MMP [44–45]. Reduction in serum C-reactive levels [48–50]. Doxycycline does not attenuate aneurysm growth [50].	Clinical trials with longer follow-up.
Anti-platelet and anti-thrombotic therapy	Limitation of aortic rupture. Reduction of aneurysm diameter [52–54].	Inconsistent data regarding aneurysm growth [56–57]. Increased risk of bleeding in the event of AAA rupture [56]. Risk of type II endoleaks in patients subjected to EVAR [61–62].	New and high-quality clinical trials are essential.
Other drugs with anti-inflammatory properties	Cyclosporin A reduces aneurysm expansion [97].	Pemirolast does not significantly affect AAA growth [95]. Lack of efficacy of canakinumab on AAA size [96].	Ongoing clinical trial testing cyclosporine A.
Metformin	Attenuation of vascular inflammation, ROS production, signalling and neovascularization [78–81].	Observational studies support the ability of metformin to ameliorate AAA progression and aneurysm-related events [75–81].	Randomised controlled clinical trials are needed to clarify this conclusion.
Stem cells	Lack of consistency among studies regarding cell types, sources, doses, and routes of administration [82].	The VIVAAA trial was prematurely interrupted. ARREST trial interim results: suppression of inflammation and reduced aortic diameter growth [90].	New clinical trials with a longer follow up.

AAA, abdominal aortic aneurysm; ACEi, angiotensin-converting enzyme inhibitors; EVAR, endovascular aneurysm repair; MMP, matrix metalloproteinase; PWRI, aortic peak wall rupture index; PWS, aortic peak wall stress; ROS, reactive oxygen species.

did not meet expectations [96]. Finally, the benefit provided by cyclosporine A, on aneurysm expansion in two experimental models [97] and its ability to inactivate cyclophilin A, which could promote aneurysm development [98], added to its immunosuppressive properties encouraged the implementation of a clinical trial analysing the efficacy of this drug in patients with small AAA; this trial seems to be in progress and unfortunately, no results have been reported (NCT02225756).

The information compiled in this section is summarised in Table 2.

Novel promising therapeutic targets

The absence of medical therapies for the management of AAA and the failure of clinical trials addressing this issue has encouraged an active investigation in search of new candidate strategies. Efforts have been directed at the mechanisms underlying the destructive vascular remodelling in AAA, which involves interrelated responses including, inflammation, ECM disruption, and medial VSMC paucity (by apoptosis, but also through necroptosis). Beyond these processes, recent insights, support the interest in new therapeutic targets, such as the sympathetic system, the crosstalk between ROS, mitochondrial dysfunction, and endoplasmic reticulum (ER) stress and the contribution of epigenetics to disease progression. Here we summarise some of the promising therapeutic approaches identified by targeting these processes (Figure 3).

The immune-inflammatory response as a therapeutic target for AAA

Vascular inflammatory cell infiltration is a consistent finding in human and experimental aneurysmal lesions. Inflammatory cells contribute to the destructive remodelling of the arterial wall and VSMC apoptosis through the release of cytokines and proteolytic enzymes and the increase in vascular oxidative stress. Although some studies suggest that immunosuppression could exacerbate aneurysm growth and promote its rupture questioning the safety of anti-inflammatory interventions in these patients [99], depletion of B cells, mast cells, neutrophils and natural

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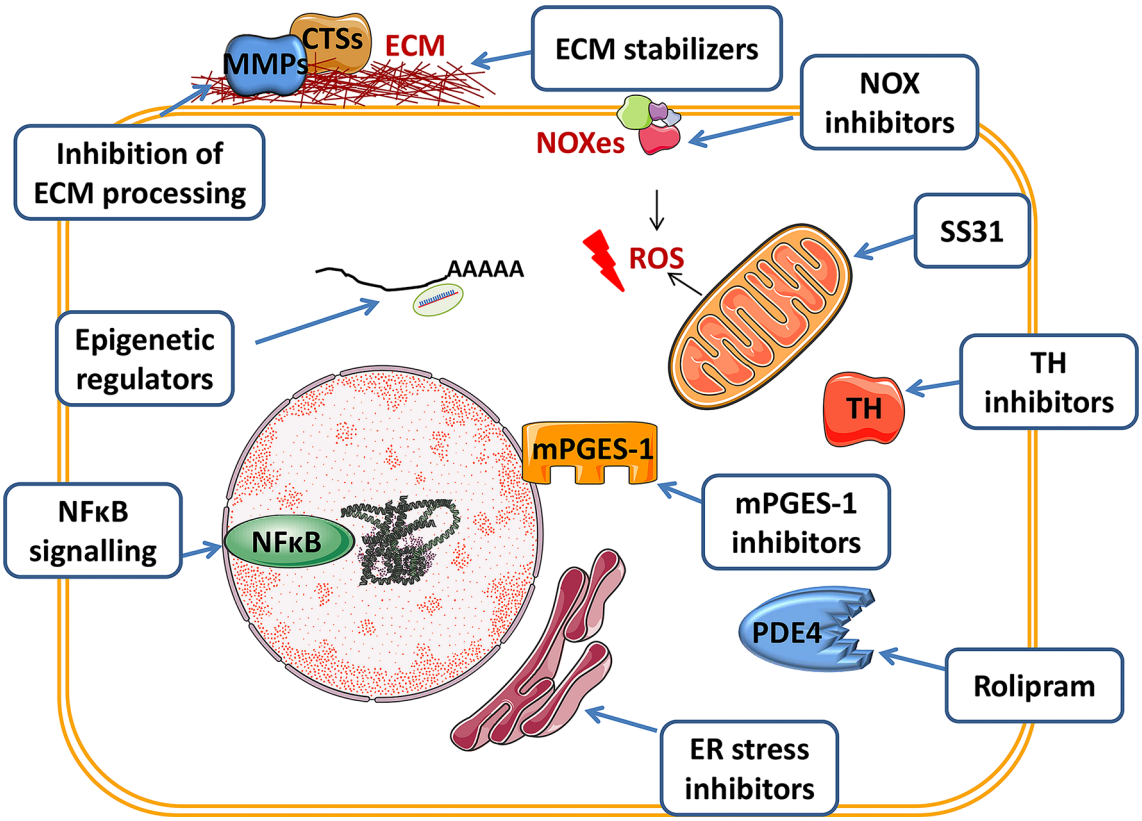

Figure 3. Promising therapeutic targets and medical interventions in abdominal aortic aneurysms (AAA)

The scheme summarises some of the candidate strategies identified in preclinical studies. The figure was partly generated using Servier Medical Art provided by Servier, licenced under a Creative Commons Attribution 3.0 unported license. CT, cathepsin; ECM, extracellular matrix; ER, endoplasmic reticulum; MMP, metalloproteinase; NFB, nuclear factor kappa B; NOX, NADPH oxidase; PDE4, phosphodiesterase 4; ROS, reactive oxygen species; TH, tyrosine hydroxylase.

killer T cells in rodents has been reported to ameliorate AAA development, while Tregs seems to play a protective role against this disease [2]. Therefore, it is tempting to speculate that targeting specific aspects of the inflammatory response might ameliorate aneurysm development, thereby representing a promising field of discovery, as discussed below.

mPGES-1 and EP4

In the synthesis of prostanoids, arachidonic acid is converted to prostaglandin H2 (PGH2) by cyclooxygenases (COXs) and further transformed into specific prostaglandins. Microsomal prostaglandin E2 synthase -1 (mPGES-1) catalyses the isomerization of PGH2 into PGE_2, which is produced in great amounts under pro-inflammatory conditions [100] and recognised as a relevant player in AAA [101–103]. Certainly, the excessive production of PGE_2 is a hallmark of human AAA. Studies in the late 1990s had already shown how PGE_2 production in AAA specimens was extremely enhanced compared with control aortas [101,102]. This was associated with an upregulation of COX2 and mPGES-1 expression in human aneurysmal samples that seems to precede maximal leukocyte infiltration, both enzymes localising to vascular cells and leukocytes [104]. Previous reports showed that the treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) in a reduced number of patients with small aneurysms led to a decrease in AAA growth rates compared with those patients non-taking NSAIDs [102], in agreement with previous studies in animal models [105,106]. However, the use of NSAIDs in humans increases aortic stiffness [107], and in patients with AAA, it is a risk for type II endoleaks after endovascular repair, as described above for anticoagulation [108]. Added to this is the predisposition to myocardial infarction and stroke associated with COX-2-selective NSAIDs [109], thereby questioning their risk/benefit and discouraging the use of these drugs in AAA. Interestingly, mPGES-1 knockdown in mice protects against AngII-induced AAA formation [110]. Therefore, mPGES-1 emerges as an interesting alternative pharmacological target particularly relevant for the management of AAA. Additionally, E-prostanoid (EP)

receptors, which mediate PGE_2 biological actions, were also augmented in human AAA [104]. Among them, EP4 is strongly induced and localises with mPGES-1 in the microvasculature of human aneurysmal lesions where it seems to mediate the proangiogenic response induced by PGE_2. Further, mPGES-1 and EP4 microvascular expression were enhanced by active smoking in patients with AAA [111]. Collectively, these data support the relevance of the COX-2/mPGES-1/EP4 axis in aneurysm neovascularisation, a process that could be involved in the progression and rupture of AAA. Certainly, EP4 seems to play a significant role in AAA, since its pharmacological inhibition in mice attenuates AAA incidence and severity, limiting vascular inflammation and ECM remodelling [112,113]. Of note EP4 inhibition not only prevents aneurysm formation but also attenuates the growth of established experimental aneurysms, more firmly supporting its translational relevance [112]. High expression of EP4 in VSMC from human AAA has been also reported and a recent study confirmed that the overexpression of this receptor in VSMC aggravates experimental AAA with enhanced infiltration of inflammatory macrophages and higher IL6 expression and MMP9 activity [114]. Further, EP4 stimulation in VSMC reduces protein levels of lysyl oxidase (LOX), a critical enzyme for the maintenance of matrix architecture [115,116], a mechanism that could contribute to aneurysm development by weakening the ECM (see below) [117]. Altogether these data support the interest of mPGES-1 and EP4 as promising targets in AAA; however, inconsistent data have been also reported since EP4 deletion on bone marrow cells fosters vascular inflammation, apoptosis and ECM remodelling and exacerbates AAA [118]. Therefore, a deeper understanding of cell-specific EP4-mediated responses will be needed to confirm whether systemic EP4 inhibition would confer protection against AAA.

PDE enzymes: PDE3 and PDE4 inhibitors

Cyclic nucleotide phosphodiesterases (PDEs) constitute a large superfamily of highly conserved enzymes (PDE1 to PDE11) that regulate cellular levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), second messengers that play a fundamental role in intracellular signalling. These enzymes are phosphohydrolases that selectively catalyse the hydrolysis and inactivation of cAMP and cGMP, thus regulating the magnitude and duration of their signalling, as well as, multiple metabolic and pathophysiological processes [119]. PDEs are grouped based on their selectivity for the substrate. While PDE3 hydrolyses cAMP and cGMP and PDE4 is the main cAMP-selective PDE, both enzymes are the major contributors to cAMP-hydrolysing activity in most cell types.

Although no data about PDE3 expression in human or experimental AAA has been provided, two independent studies demonstrated that the PDE3 inhibitor cilostazol, an antiplatelet agent used for the treatment of peripheral artery disease and stroke, suppresses AAA in preclinical models, attenuating vascular inflammation, MMP activity, and ROS production [120,121]. Unfortunately, the effectiveness of cilostazol against AAA has not been addressed in clinical trials.

Additionally, we have recently involved PDE4B in AAA [122]. This specific PDE4 isoform is significantly up-regulated in human and experimental aneurysmal lesions where localises to the inflammatory infiltrate. In fact, PDE4B is the main PDE4 subtype expressed in inflammatory cells and critically influences immune and inflammatory responses, thereby emerging as one of the main interesting targets against a wide range of disorders, specifically, inflammatory and autoimmune diseases [123,124]. Moreover, we found that PDE4D expression was similar in healthy aorta and AAA, both in humans and in the murine model, thus supporting that, while PDE4B could be involved in the pathophysiology of the aneurysm, the contribution of PDE4D would be secondary. However, a recent study reported no differences in vascular PDE4B expression in both patients with AAA and mouse aneurysmal lesions [125]. Surprisingly, this work detected significant up-regulation of PDE4D in aneurysmal VSMC and found that the cell-specific deletion of PDE4D abrogated the development of experimental AAA, further reducing blood pressure levels. The discrepancies between both reports would be related to the low number of human samples and the almost significant difference in the age between control and AAA groups in the study conducted by Gao et al., to the heterogeneity of human aneurysmal lesions, and, regarding preclinical studies, to differences in the mouse models of AAA [125]. Anyway, both studies demonstrated how PDE4 inhibition with rolipram significantly attenuated aneurysm formation, preserving elastin integrity and normalising MMP2 activity [122,125]. Further, Varona et al demonstrated that rolipram ameliorated vascular inflammatory infiltration and oxidative stress [122]. Therefore, and beyond the discrepancies between both studies, these data suggest that the selective inhibition of PDE4 activity could provide a benefit in vascular diseases such as AAA, as suggested by the low rate of cardiovascular events detected in patients with chronic obstructive pulmonary disease treated with roflumilast [126]. However, severe side effects are associated with non-isoform-specific PDE4 inhibitors, mainly related to the inhibition of the PDE4D subtype. In this context, it is tempting to speculate that the anti-inflammatory response provided by selective PDE4B inhibitors might benefit AAA patients [127,128]. Worthy of mention is the PDE5 inhibitor sildenafil, which inhibits cGMP hydrolysis and has been found to exacerbate the progression of experimental aneurysms [129]. Further, its abuse has been clinically

Clinical Science (2023) **137** 1167–1194
https://doi.org/10.1042/CS20220795

related to aortic dissections [130]. Therefore, the prescription of sildenafil in patients with AAA should be considered carefully.

Inflammatory signalling

Accumulated evidence has highlighted the critical involvement of inflammatory signalling pathways in the control of vascular remodelling underlying AAA progression and their therapeutic potential. Nuclear factor (NF)κB, c-Jun N-terminal kinase (JNK), Janus kinase/signal transducers and activators of transcription (JAK/STAT) and WNT signalling are some of the key signal integrators controlling vascular inflammation that have been studied as novel targets for AAA therapy.

The activation of the NF-κB family and the consequent regulation of downstream targets triggers different processes such as innate and adaptive immunity, and cell survival, differentiation, and proliferation and regulates cellular responses to stress, hypoxia, stretch and ischaemia, being critical in vascular diseases such as atherosclerosis and AAA [131]. Studies developed in the first decade of this century focused on NFκB and ETS, transcription factors involved in the control of inflammation and MMP expression, and their role in AAA. Based on electrophoretic mobility shift assays, these authors reported the striking activation of both NFκB and ETS in the neck of human AAA, which is the most active region of aneurysmal lesions. Interestingly, decoy oligodeoxynucleotides (ODN), which competed with the binding of these transcription factors to their respective response elements and suppress their signalling, achieved a significant benefit on aneurysm progression in two experimental animal models. This strategy decreased aneurysm size, preserved elastic fibre integrity, reduced MMPs expression and limited macrophage infiltration, thus suggesting the potential of decoy-based therapies in AAA and the interest of targeting these signalling pathways. However, special consideration should be given to the divergent functions of NFkB in the cardiovascular system, playing both beneficial and detrimental roles depending on the cellular and physiological context. For example, NFκB activity in macrophages triggers anti-atherogenic responses whereas in endothelial cells is a pro-atherogenic factor [131]. Whether this dichotomy also operates in AAA is uncertain, but these data strongly support that approaches targeting NFκB therapeutically in human AAA should be carefully considered and would benefit from the development of cell-specific inhibitors.

The dysregulation of JNK signalling is another feature of human AAA [117]. Certainly, human AAA specimens showed high levels of phosphorylated JNK. Through several experimental approaches in two animal models, the authors showed that this route is essential for the development of AAA by activating a coordinated response that contributes to the destructive remodelling of the ECM, encompassing both the up-regulation of MMP9 activity and the suppression of LOX. More interestingly, the pharmacological inhibition of JNK with SP600125 abrogated aneurysm development and further regressed established AAA, thereby highlighting that targeting JNK could allow the repair and stabilization of the ECM in this disorder, being a solid candidate for pharmacologic intervention. Similarly, in a mouse model of AAA, higher JNK1 expression associated with enhanced MMP levels has been reported in males compared with females, suggesting that this might be partially responsible for the differential incidence of AAA between genders [132]. Although further research will be needed to confirm this hypothesis in humans, the higher JNK activity reported in aneurysms from males might be related to the lower vascular LOX expression in men with AAA compared with women that seem to underlie the sexual dimorphism of this disease [133]. Additionally, cJun/AP-1 and the C/EBP homologous protein (CHOP) that mediates cell apoptosis, were simultaneously induced in the aneurysmal lesions from Ang II-infused ApoE$^{-/-}$ mice. In fact, cJun/AP-1 regulates CHOP transcriptional activity, thus linking this signalling pathway not only to inflammation and ECM remodelling but also to the apoptosis-mediated loss of VSMC characterising this disease [134]. Interestingly, the inactivation of JNK activity is one of the common mechanisms underlying the attenuation of AAA achieved by either the genetic ablation of microRNA-33, a critical microRNA in the pathogenesis of this disease (see below) [135], an Ang II peptide vaccine [136] or by the biphosphonate zoledronate [137], supporting again the interest of this signalling cascade as a therapeutic option in AAA.

The JAK/signal transducer and activator of transcription (JAK/STAT) pathway also emerge as an appealing medical target for AAA. JAK/STAT signalling is overactivated in human AAA [138] and pSTAT3 levels are increased in human and murine aneurysmal lesions [139]. Accordingly, the benefit provided by several direct or indirect inhibitors of the STAT3 pathway has been reported in different animal models of AAA [139–142]. Conversely, STAT3 signalling has also been claimed as a critical factor for the maintenance of vascular integrity. In fact, deficiency of STAT3 in humans leads to vascular abnormalities and a high incidence of aneurysms [143] and the *in vivo* inhibition of this pathway by overexpressing SOCS3 increased the severity of aneurysms in a non-hyperlipidemic mouse model [143,144]. This effect seems to be cell-specific, linked to T-cells and the potential protective role of interleukin-17 on this disease [144]. Recent research highlights that STAT3 regulates the balance between the destruction and preservation of the aortic tissue and that depending on the cell type (macrophages vs VSMC) the inhibition of STAT3 results in an exacerbated

incidence of aortic dissections or in a protective response that reinforces aortic biomechanics [145]. Therefore, there is already much to learn about this pathway to develop safe and effective therapeutic strategies targeting JAK/STAT signalling.

In the last years, Wnt signalling has aroused the interest of the scientific community. This pathway is aberrantly reactivated in several disorders, including cardiovascular diseases. Multiple elements of this pathway are dysregulated in human and experimental aneurysms, in which high levels of the transcriptionally active form of β-catenin have been found, pointing to an overactivation of the Wnt/β-catenin pathway in AAA [146]. This route has been involved in the control of monocyte migration and adhesion [147,148], but beyond its impact on inflammation, the Wnt/β-catenin cascade enhances MMP expression and influences VSMC homeostasis [149–152], which emphasises the potential of targeting this pathway as a therapeutic option for AAA. However, the effective blockade of the Wnt/β-catenin signalling pathway with either the porcupine inhibitor LGK974 or PRI-724, which disrupts the interaction between β-catenin and the (CREB)-binding protein, proved ineffective in limiting aneurysm formation induced by AngII-infusion in ApoE$^{-/-}$ mice. Although PRI-724, slightly slowed down the progress of AAA and improved the severity of aneurysmal lesions, no clear overall benefit on aortic diameter and AAA incidence were detected and, therefore, these data advocate for targeting specific elements of this signalling route as a possible strategy for the management of this disease. Previous studies reported that the Wnt/β-catenin inhibitor sclerostin limits aneurysm formation in an experimental model [153], while recently a comparable favourable outcome was obtained by the deletion of CNN4, a Wnt signalling target gene that exerts pro-inflammatory responses in different pathological scenarios [154]. Similarly, the benefit on AAA progression provided by miR-124a has been related at least in part to the regulation of Wnt/β-catenin signalling [155]. Multiple targetable candidates among Wnt pathway components could be potentially approached based on human data [146], supporting the rationale for further research in this field.

Finally, recent research strengthens the view that the engagement of immunoglobulin G (IgG) Fc receptors (FcγR) by immune complexes is relevant in AAA. In fact, FcγR expression was enhanced in human and mouse aneurysmal lesions, while FcγR knockdown decreased AAA incidence and aortic dilation, preserving elastin integrity and VSMC content and limiting vascular inflammation and oxidative stress, thus suggesting that the IgG-FcγR-axes might represent a therapeutic target for this disease [156,157].

Targeting ECM to preserve vascular integrity

ECM disruption contributes to the destructive remodelling of the aortic wall that features AAA. Thus, it has been speculated that limiting ECM degradation, for example targeting its proteolytic processing, might ameliorate disease progression. Further, strategies aiming at stabilising the ECM has been also proposed as an alternative to prevent aortic wall failure in AAA, as detailed below.

ECM Proteolytic Degradation

ECM remodelling in AAA involves the activation of several families of extracellular proteases such as MMPs but also of serine and cysteine proteases, all of them enzymes that degrade the main structural components of the arterial wall, namely collagen and elastin. The MMP-mediated proteolytic degradation has been extensively studied and identified as a critical step in the gradual weakening and instability of AAA, being MMP2 [158,159], MMP9 [159,160], and MMP12 [161], the main MMPs linked to this process. As it has already been discussed, tetracyclines and, in particular, doxycycline emerged as a non-selective MMP inhibitor that reduces the incidence of AAA in experimental models. However, studies in patients were inconclusive and questioned the usefulness of doxycycline as a therapeutic option for the management of AAA. Additionally, although more than 50 broadspectrum MMP inhibitors have been developed and tested in clinical trials for different disorders, all of them failed as therapeutic tools due to the lack of specificity and the occurrence of musculoskeletal side-effects, among others [162]. While doxycycline, formulated at a sub-antimicrobial dose, is the only MMP inhibitor approved by the FDA for periodontal disease, a new generation of MMP inhibitors more selective and with improved pharmacokinetic profiles have advanced to clinical trials for different diseases [163], and therefore the door is still open for new clinical trials testing MMP inhibitors in AAA.

Cysteine and serine proteases have also been involved in the pathogenesis of AAA. Early studies in human atherosclerotic and aneurysmal lesions revealed that the expression of elastolytic cysteine proteases, such as cathepsins L, S and K [164–166], is significantly increased, while that of cystatin C (a cysteine protease inhibitor) is markedly decreased. Similarly, enhanced levels of mast cell chymase and tryptase have been reported in human AAA [93,167].

The direct participation of these enzymes in AAA has been demonstrated by gene-knockdown in preclinical models [168–170], studies that linked the disturbed expression of these proteases not only to the ECM disarrangement but also to the inflammatory response, affecting chemotaxis and chemokine production, VSMC apoptosis, angiogenesis and protease activation. Interestingly, serum cathepsin S, chymase and tryptase levels correlate with the aneurysm

Clinical Science (2023) **137** 1167–1194
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growth rate in patients with AAA, while cystatin C levels seems to be inversely associated with abdominal aortic diameter [93,167,171,172], suggesting that they can serve as novel biomarkers for this disease. Altogether these data emphasised that the imbalance between vascular cysteine and serine proteases and cystatin C could promote proteolysis and favour aneurysm progression and that the maintenance of the equilibrium among these enzymes could be a therapeutic strategy. This research underscores the interest of chemical inhibitors of cathepsins as pharmacological tools for AAA, now being tested in experimental models with promising results [173–175].

Serine proteinases involved in fibrinolysis, specifically, tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA), have been also related to AAA due to their role in inflammation and proteolysis. Both uPA and tPA activate plasminogen to plasmin, which in turn initiates a proteolytic cascade leading to MMP activation and ECM degradation, which might contribute to AAA. Expression of uPA increases in human and experimental aneurysmal lesions [176,177], while uPA deficiency protects against aneurysm rupture in AngII-infused ApoE$^{-/-}$ mice, thus suggesting an active contribution of uPA to this disease [178]. Consistently, in this model, the local overexpression of the uPA inhibitor, plasminogen activator inhibitor-1 (PAI-1), limited aneurysm expansion [179]. However, conflicting results were subsequently published, showing that deficiencies of either uPA or its receptor (uPAR) did not influence the incidence or size of aneurysmal lesions in LDL receptor knockout mice challenged with Ang II nor enhanced the rate of AAA rupture [180]. Furthermore, bone marrow transplantation studies demonstrated that the increased AAA rupture could be attributed to the lack of uPA in hematopoietic cells and suggests that the absence of uPA affects the resolution of transmural thrombi while promoting aortic rupture, excluding an impact on MMP activity [180]. In view of these discrepancies, further research will be needed to clarify the contribution of the uPA–uPAR system to AAA.

Lysyl oxidases (LOXs) and other elastogenic proteins

The LOX family is comprised of five closely related ECM enzymes, involved in the covalent cross-linking of collagen and elastin, which conditions the tensile strength and elastic properties of connective tissues [115,116,181]. Early studies in the 1990's suggested that LOXs are critical to preserving the structure and mechanical properties of the aorta and that a decrease in LOX expression and activity is associated with the development of experimental aneurysms [117,182]. Subsequently, two independent groups reported that the genetic inactivation of the archetypal LOX form, but not that of other isoenzymes of this family, is lethal and associates with large aneurysmal lesions and aortic dissections [183,184]. In fact, the pharmacological inhibition of LOX activity induces AAA in different animal models [117,182,185,186], while interestingly, the local overexpression of LOX by periadventitial adenoviral delivery attenuates the progression of experimental aneurysms. Beyond EMC maturation, LOX also attenuates vascular inflammation through a reduction in MCP-1 secretion, limiting macrophage infiltration and JNK activation [187,188], further supporting the interest of LOX as a pharmacological target for this disease. Unfortunately, evidence about the contribution of downregulation of LOX to human disease is scarce, mainly due to the lack of human samples corresponding to the early stages of the aneurysmal disease, when surgery is not recommended. Nevertheless, and because AAA is considered a local manifestation of a general defect in the vasculature [1,189], it has been suggested that aneurysmal disease could be associated with changes in the expression pattern in other vascular beds. In particular, the proteomic profile of the internal mammary artery from patients with AAA reflects a significant upregulation of LOX and other elastin-related molecules, which was regarded as a compensatory response to protect vascular wall integrity [190]. More interestingly, recent findings have involved LOX in the sexual dimorphism of AAA [133]. The authors found lower vascular LOX expression and activity in males, both in human and animal models and determined that an androgen-mediated inhibition of LOX activity underlies the higher susceptibility to AAA exhibited by males, supporting that normalising LOX could abolish sexual dimorphism and limit AAA in males. Thus, LOX expression/activity could critically participate in AAA development which would support control of LOX activity as a strategy to preserve vascular integrity and curtail aneurysm progression. Further investigations will be needed to provide convincing proofs of the feasibility of this approach.

Besides LOXs, elastic fibre assembly is coordinated by fibulin-5 (FBLN5), an integrin-binding matricellular glycoprotein, which is critical for elastogenesis, but also participates in cell–cell and cell–matrix communication and controls vascular cells adhesion, proliferation, migration, and survival [191,192]. In the vascular wall, FBLN5 is responsible for the preservation of vascular integrity after injury avoiding anomalous remodelling [193,194]. Interestingly, in human aneurysmal lesions, the expression of FBLN5 is significantly decreased [195], while studies in AngII-infused C57BL/6J mice demonstrated the contribution of FBLN5 downregulation to aortic dilation. Certainly, vascular FBLN5 knockdown circumvented the intrinsic resistance of the C57BL/6J strain to AngII-induced dilation, increasing aortic diameter and the expression of inflammatory mediators [195]. As discussed below, the reduced

expression of FBLN5 in AAA is related to the inflammatory component of the disease and epigenetic regulation mediated by the HDAC/SOX9 axis. The authors concluded that preserving normal FBLN5 vascular expression could prevent aortic wall failure and become a promising therapeutic strategy in AAA.

ECM stabilising agents

Agents that stabilise the ECM and prevent the progressive degradation of the vascular wall in AAA have been investigated in the last years with encouraging results. Among them, pentagalloyl glucose (PGG) stands out due to its safety. PGG is a tannic acid derivative that acts as an elastin-stabilising polyphenol [196]. The ability of PGG to stabilise elastin enables this compound to improve tissue biomechanical stability, a feature that has been exploited in tissue-engineering for the development of vascular grafts and that has prompted its application to restrict aortic aneurysm growth. The first evidence supporting PGG for the treatment of AAA was reported in 2007 when the benefit of this compound ameliorating $CaCl_2$-induced aneurysms in rodents was demonstrated [197]. In this study PGG preserved the integrity of elastic lamellae in abdominal aorta despite no affected inflammation or MMP levels [197]. Since then, multiple investigations have confirmed the ability of PGG inhibiting AAA expansion in different experimental models [198,199] and have addressed strategies to specifically target PGG to aneurysmal lesions (including the use of PGG-loaded nanoparticles) [200]. The benefit conferred by PGG could also be due to the increase of LOX expression that would additionally contribute to ECM stabilisation [201]. Of note, PGG exhibits anti-inflammatory, vasodilatory and ROS scavenging properties and behaves as a non-competitive inhibitor of thrombin [196]. Whether these effects could also account for the favourable impact of PGG on experimental AAA and whether it could be useful in clinical practice deserves further research.

Loss of VSMC by Necroptosis

Depletion of VSMC is one of the main processes featuring AAA that contributes to aortic wall weakening and impairs ECM production and repair. VSMC loss has been classically attributed to apoptosis; however, in the last years, necroptosis (also known as programmed necrosis) has emerged as a critical phenomenon in VSMC paucity and as a new target for therapeutic intervention. This programmed cell-death pathway is orchestrated by the kinases RIP1 and RIP3 [202], both of them elevated in VSMC in human and experimental aneurysmal lesions. Noticeably, the deletion of RIP3 abrogated AAA formation and impaired the p65-dependent inflammatory response in the elastase-induced mouse model [203]. Mixed lineage kinase domain-like pseudokinase (MLKL) and calcium/calmodulin-dependent protein kinase II (CaMKII) are downstream effectors of RIP1-dependent necroptosis in AAA. Interestingly, pharmacological inhibition of necroptosis by targeting RIP1 or RIP3 ameliorates aneurysm expansion and even stabilises pre-existing aneurysms attenuating inflammation and inducing ECM repair [203,204], while, recently, the protective role of IL-37 on aneurysmal disease has been related to its ability to suppress RIP3-mediated necroptosis [205]. These findings have encouraged active research aiming at characterising the regulatory mechanisms underlying RIP3 upregulation in AAA [206], which will provide grounds for new therapeutic strategies for this disease.

Targeting epigenetic mechanisms in AAA

Epigenetics refers to those changes in the genome that do not involve modifications in the DNA sequence and that often occur in response to environmental cues or lifestyle factors. Epigenetic mechanisms of gene regulation encompass (i) histone modifications and chromatin remodelling, (ii) DNA methylation, and (iii) RNA-based mechanisms. Epigenetics drives the maladaptive tissue remodelling response underlying cardiovascular diseases. Accumulating evidence supports that epigenetics plays a central role in AAA and that its control may hold potential for therapeutic intervention [207,208]. In this section, we will review the most significant findings supporting the relevance of pharmacological interventions targeting the epigenetic landscape in AAA.

DNA methylation

DNA methylation involves the addition of a methyl group to the 5′ position of cytosine residues at cytosine preceding guanosine (CpG) islands. Most CpG islands are sites of transcription initiation and promoter methylation usually results in reduced accessibility of transcription factors to *cis*-DNA-binding elements, thereby suppressing transcription. Interestingly, the methylation pattern is dynamic and susceptible to changes in response to ageing and lifestyle factors such as smoking, both being major risk factors of AAA [209]. The DNA methylation status relies on the balance between DNA methyltransferases (DNMT), responsible for DNA methylation, and the activity of the ten–eleven translocation (TET) family of enzymes that demethylate CpG islands. Analysis in peripheral blood mononuclear cell DNA from healthy controls and patients with AAA, revealed significant differences in DNA methylation [210]. AAA is related to global hyper-methylation, while the methylation status positively correlates with aortic diameter [211].

Clinical Science (2023) **137** 1167–1194
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Further, Tonghill et al identified gene-specific changes in DNA methylation in VSMC from human aneurysmal samples. Certainly, the decrease of both smooth muscle 22α (SM22α) and sclerostin, which are characteristic of human AAA and contribute to aneurysm development, is derived from their promoter hypermethylation [153,212]. Likewise, a cohort study from a population-based screening program in Sweden did observe higher global DNA methylation in patients with AAA and a linear association with baseline aortic diameter, although no significant association between DNA methylation and AAA growth was found during follow-up [213]. In turn, the DNA methylation rate and the expression of several DNMTs were increased in Tregs from patients with AAA [214]. Similarly, DNA methylation was markedly disturbed in aortas of patients with acute aortic dissection and associated with the altered gene expression pattern featuring this disorder [215]. Because DNA methylation is a dynamic process, therapeutic approaches aiming to attenuate the aberrant methylation status in AAA could be a useful strategy for this disease, however, no experimental data supporting this hypothesis are currently available, while the severe side effects of hypomethylating agents are a major pitfall for these drugs.

Histone post-translational modifications

Histone post-transcriptional modifications conditions the structure and packaging of chromatin, thereby controlling the accessibility of transcription factors to DNA. Acetylation and methylation are the most extensively studied histone modifications. Histone methylation, regulated through histone methyltransferases and histone demethylases, can lead to both transcriptional activation and repression, while promoter acetylation usually associates with transcriptional activation.

Histone methylation seems to play an essential role in macrophage-mediated inflammation in AAA. In particular, the histone demethylase Jumonji domain-containing protein D3 (JMJD3) is increased in infiltrating myeloid cells from human aneurysmal lesions resulting in an induction of the inflammatory immune response. Mechanistically, JMJD3 limits H3K27 trimethylation on pro-inflammatory cytokine promoters rendering them accessible to NFkB binding and thereby inducing the inflammatory response triggered by these cells [216].

The balance between histone acetyltransferases (HATs) and histone deacetylases (HDACs) controls the degree of histone acetylation. Notably, in the vasculature, HDACs strongly influence gene transcription and affect the expression of genes critically involved in essential processes underlying AAA development, such as ECM remodelling, inflammation and VSMC differentiation and function. Increased mRNA levels of specific HDACs have been reported in Tregs from patients with AAA [214]. Similarly, the expression of class I and II HDACs (HDACs 1, 2, 4 and 7) was significantly augmented in aneurysmal lesions from AAA patients, where they localize to both VSMC and infiltrated inflammatory cells and associated with a consequent decrease of vascular histone H3 acetylation (H3K18) [217]. Interestingly, in a mouse model of AAA that also exhibits reduced histone acetylation and higher HDAC expression resembling human disease [217,218], the administration of MS-275 (a class I HDAC inhibitor) or MC-1568 (that inhibits class II HDACs), attenuated the incidence and severity of AAA, normalised aortic diameter and reduced AngII-induced mortality, limiting vascular and systemic inflammation and also ECM destructive remodelling [217]. Among other effects, HDAC inhibitors prevented the cytokine-mediated reduction of FBLN5, an essential protein for elastic fibre formation and one of the most downregulated proteins in human AAA [195,219]. By *in vivo* approaches, Orriols et al. demonstrated the critical contribution of FBLN5 knockdown to AngII-induced aortic dilation and vascular inflammation identifying the involvement of a SOX9/HDAC-dependent mechanism in the downregulation of FBLN5 by inflammation. Thus, preserving FBLN5 could prevent the disorganization of ECM induced by inflammation in AAA [195]. Further, and considering that class I and II HDAC inhibitors have been proven effective in several types of cancer, these studies suggest that HDAC inhibitors could be repurposed for the treatment of AAA. However, caution should be adopted, since inconsistent data have been also reported in human aneurysmal disease, with higher acetylation of the histone substrates H3K9, H3K18 and H3K14 associated with enhanced expression of vascular HATs [220]. Further, it is interesting to note that sirtuin 1 (Sirt1) activity is decreased in aortic specimens from patients with AAA [221]. Sirt1 is an HDAC class III member that participates in the suppression of inflammation. The study by Horimatsu et al. found that the hypolipidaemic agent niacin protects against AAA formation through the increase in Sirt1 activity, in agreement with previous studies reporting that the macrophage-specific deletion of Sirt1 promotes aneurysm formation [222], thus suggesting that Sirt1 agonism could become a promising therapeutic strategy for AAA.

Noncoding RNAs

Noncoding RNAs do not influence chromatin architecture but participate in post-transcriptional regulation of gene expression. Noncoding RNAs encompass small RNAs, mainly microRNAs (miRNAs) and long noncoding RNAs (lncRNAs).

The tissue- and plasma-specific miRNA signature in human AAA has been characterised by high-throughput approaches. Two independent studies [223,224], revealed the significant upregulation in aneurysmal lesions of microRNAs related to fibrosis (miR-29), inflammation (miR-124a, miR-146a, miR-155, and miR-223) and endothelium (miR-126, let-7 family members, and miR-21). Further, miR-30c2, miR-204, miR-133a, and miR-133b were downregulated associated with a consequent increase in their target genes involved in apoptosis and inflammation, fundamental processes in AAA pathogenesis [223]. The increase of miR-155 in human AAA was confirmed by subsequent studies [225] was associated with the down-regulation of its target genes CTLA4 and SMAD2, critically involved in the immune response. In turn, miR-21, which influences VSMC proliferation and apoptosis, is also increased in both human and experimental aneurysmal lesions. Probably, this is a compensatory response to limit aneurysm expansion, since in murine models miR-21 overexpression prevented AAA progression, while its blockade augmented aortic diameter [226]. Interestingly, miR-33, which is highly expressed in central zones of human AAA compared with marginal areas, participates in the control of vascular inflammation inducing a proinflammatory M1 macrophage phenotype, while it is knockdown ameliorates experimental AAA [135]. Regarding miR-29, increased aortic expression of miR-29 family members, along with decreased mRNA levels for its targets genes, encoding for ECM proteins, have been reported in two murine models [227], in which the *in vivo* blockade of this miRNA reduced aneurysm growth [227,228]. Because miR-29 inhibition associates with an enhanced expression of ECM components the risk of fibrosis by targeting this miRNA cannot be overlooked.

Progression of experimental AAA is also related to a downregulation of the miR-23b-24-27b cluster, being miR-24 significantly inhibited in human AAA, where its level inversely correlates with aneurysm size. miR-24 was identified as a critical regulator of vascular inflammation in AAA by targeting chitinase 3-like 1 (Chi3l1) in macrophages, VSMC and endothelial cells, suggesting that the decrease of miR-24 contributes to aneurysm growth and that both miR-24 and CHI3L1 could become novel plasma biomarkers of AAA disease progression and therapeutic targets for this disease [229].

Of note, this is only a small sample, likely the most translationally relevant, of the huge amount of information about miRNAs and their involvement in the pathogenesis of AAA, indicative of the complexity of this aspect of the disease [230,231]. There is an evident need for broader knowledge to more clearly uncover how miRNAs influence vascular remodelling in AAA and their real therapeutic value. miRNAs have emerged as highly interesting pharmacological tools to restore cell homeostasis, but an additional challenge for therapeutics is how to interfere with miRNA function in an effective and safe manner. There are still important technical concerns to overcome in this field, however, clinical trials assessing miRNA-based interventions have been launched for different disorders, and some of them have been approved by FDA, including two therapies against cardiovascular diseases [232,233].

In turn, LncRNAs comprise a more heterogenous group of RNA molecules, larger than 200 nucleotides, that modulate gene transcription through a variety of ways still incompletely characterised, [230]. Concerning AAA, numerous studies have shown the crucial role of lncRNAs in different processes underlying aortic growth, but only a few of them have been functionally characterised. Results from *in vivo* studies in animal models have analysed the participation of H19, GAS5, PVT1, XIST, SENCR, MYOSLID, SMILR, and NEAT1 in AAA pathophysiology [230,234,235]. In fact, silencing these lncRNAs reduces AAA formation and attenuates aortic diameter by different mechanisms, like limiting the MMP-dependent proteolytic degradation of the aortic wall, reducing the expression of inflammatory mediators and attenuating apoptosis [236–239]. Although these data suggest the utility of lncRNAs as therapeutic targets, similar to miRNAs there are several concerns to translate them to clinical research. However, there is currently a huge interest in targeting these molecules in cardiovascular diseases with some trials testing their utility as biomarkers and some noncoding RNA-based therapies being analysed in preclinical trials. These studies encourage future research in the field of AAA [240,241].

Other epigenetic mechanisms

Beyond these aspects related to histone post-translational modifications, DNA methylation, and noncoding RNAs there is much to be learned about epigenomics in AAA. Intensive research on this issue is being undertaken with appealing results. The bromodomain extra-terminal (BET)-containing a family of epigenetic reader proteins emerges as a novel epigenetic player orchestrating complex transcriptional programs in cardiovascular homeostasis and more specifically in AAA, for which targeting BET could become an attractive pharmacological strategy [242,243]. More interestingly, recent research identified ATP-dependent chromatin remodelling enzyme complexes as critical players in AAA. Endothelial-specific deletion of Brahma related gene 1 (Brg1), a chromatin remodelling protein, attenuates AAA [244]. Similarly, BAF60c and BAF60a, unique subunits of the SWI/SNF (switch/sucrose nonfermentable) chromatin remodelling complex were identified as important regulators of VSMC homeostasis with opposite functions, underscoring their critical contribution to the control of vascular inflammation and ECM remodelling in AAA and

Clinical Science (2023) **137** 1167–1194
https://doi.org/10.1042/CS20220795

the potential of targeting BAF60-mediated epigenetic modifications for this disease [245,246]. Further research is obviously guaranteed.

The sympathetic system as a new target in AAA

The vascular and nervous systems are in close connection and emerge as critical communication systems in mammals, existing in coordinated mutual cross-talk with important pathophysiological repercussions [247]. The disturbance in the sympathetic nervous system has a fundamental role in the development of highly prevalent cardiovascular diseases including hypertension, heart failure and myocardial infarction [248,249]. The contribution of the sympathetic system to aortopathies such as AAA is less characterised, although progress has been made in the last few years, highlighting its interest as a new pharmacological target for these patients. Certainly, the occurrence of human thoracic aortic dissections has been related to an increase in sympathetic activity, while sympathetic hyperactivity and aortic sympathetic nerve sprouting have been reported in these patients, suggesting that the sympathetic nervous system may modulate both functional and structural properties of the aorta [250,251]. In fact, in aortic aneurysms, catecholamines control TGFβ signalling, attenuating VSMC proliferation and promoting apoptosis and thereby affecting vascular integrity. Further, it has been recently reported that local sympathetic denervation ameliorates experimental aneurysms [252]. In agreement, high-throughput studies in a new mouse model that overexpresses the neuron-derived orphan receptor-1 (NOR-1) in the vascular wall and reproduces the main features of human AAA, suggested the upregulation of genes involved in the tyrosine hydroxylase (TH) pathway that leads to the synthesis of catecholamines [253]. By a thorough analysis of human and murine aneurysmal lesions, we uncovered the up-regulation of several components of this signalling route in AAA and evidenced that TH localises to vascular innervations, inflammatory cells and some scattered VSMC in these samples. More interestingly, these studies provided sound evidence for the benefit of TH inhibition attenuating aneurysm formation [254,255]. The administration of α-methyl-p-tyrosine (AMPT), an orally available competitive inhibitor of TH, which decreases the endogenous levels of catecholamines, showed that the blockade of this pathway protected against AngII-induced AAA in two experimental models, normalising MMP expression and activity, preserving elastin integrity and limiting vascular inflammation and oxidative stress. Although it was developed as an antihypertensive drug, AMPT is ineffective against essential hypertension, and it is exclusively indicated for the treatment of pheochromocytoma and other rare tumours that produce excessive amounts of catecholamines (DEMSER). Of note, the association of pheochromocytoma with AAA has been reported, thus supporting again that catecholamine overproduction might promote aneurysm development and growth [256]. Therefore, these data support that TH inhibition could become an interesting approach for the treatment of AAA. Because of the short half-life and the central-adverse effects of AMPT, further research will be needed for the development of a new generation of TH inhibitors with improved pharmacokinetics and safety for the management of AAA.

Reactive oxygen species (ROS), endoplasmic reticulum (ER) and mitochondrial stress: potential targets in AAA

The implication of vascular oxidative stress in the pathogenesis of AAA has been extensively documented [257,258]. The vascular inflammatory environment critically contributes to the augmented ROS production, which, in turn, exacerbates the recruitment of inflammatory cells in a reciprocal feedback loop, thereby contributing to AAA progression [259]. Human studies have found a negative correlation between antioxidant consumption and the size of AAA, while a positive relationship was reported between aneurysm diameter and markers of lipid peroxidation, suggesting that antioxidant therapy might be beneficial for these patients [260]. NADPH oxidase is the major source of vascular ROS and increased O_2^- levels coupled with higher NADPH oxidase activity, and enhanced expression of the $p47^{phox}$ and $p22^{phox}$ subunits have been described in human AAA [257,261]. Accordingly, $p47^{phox}$ knockdown attenuates experimental aneurysms [262], and subsequent studies also supported the contribution of NOX2-derived ROS to this disease [84]. Therefore, NADPH oxidases arise as promising therapeutic targets for limiting aneurysm progression and rupture through the reduction of oxidative stress [263]. However, ROS also play essential functions in cellular signalling and homeostasis, which explains the failure of clinical studies testing the potential benefit of antioxidant supplements for cardiovascular diseases [264]. In this scenario, and to avoid serious undesired effects, huge efforts should be made for the development of isoform- and cell-specific NADPH oxidase inhibitors, whose impact on aneurysm growth will surely be addressed in the future.

Oxidative stress is closely related to the induction of endoplasmic reticulum (ER) stress, which is involved in the pathogenesis of several cardiovascular diseases [265–267], including human AAA and other aortopathies [261,268]. Certainly, analysis in a large cohort of patients with AAA reported enhanced vascular expression of activating transcription factor 6 (ATF6), IRE-1, active X-binding protein 1 (XBP-1) and the pro-apoptotic factor CHOP, while no differences for elements of the ATF4 axis of the ER stress response were detected at the end stage of AAA [261].

In agreement, classic ER stress inhibitors reduced aortic diameter and the incidence and severity of experimental aneurysms, attenuating inflammation and vascular remodelling [139,269,270]. Further, it should be highlighted that under pathological conditions the cross-talk between mitochondria and the ER promotes mitochondrial ROS generation and mitochondrial dysfunction [271,272]. It has been described that the expression of transcription factors that activate mitochondrial biogenesis and regulate mitochondrial function (PGC1α, NRF1 and TFAM), as well as that of Cyt B and Cyt C oxidase, are decreased in human aneurysmal specimens, accompanied by a reduction in the mitochondrial mass [261]. Consistent with these data, another study reported a decrease in PGC1α in the medial wall of the human aneurysmal aorta [273]. Additionally, mitochondria-dependent ROS/apoptosis activation plays a critical role in the progression of AAA in animal models of the disease [269,274]. Interestingly, the inhibition of mitochondrial stress by the mitochondria-targeted tetrapeptide SS31 prevented aneurysm formation in AngII-infused ApoE$^{-/-}$ mice. Reduced ROS production and vascular inflammation, but also an attenuation of ER stress accounted for the benefit provided by SS31. Altogether, these results reinforce the concept that the maintenance of mitochondrial homeostasis could be an interesting therapeutic strategy in AAA and support that pharmacological strategies aiming at alleviating both mitochondrial and ER stress may hold a promise to halt aneurysm progression and prevent its rupture.

Concluding remarks

Multiple potential medical targets for AAA have been identified in preclinical approaches mainly in rodents. The studies included in this revision are only a small part of the titanic efforts made in this field. However, the translation of these experimental insights into the clinics have utterly failed and the main reason for this failure might lie in the critical divergencies between humans and murine models regarding inflammatory/immune and metabolic responses [275,276]. Being a chronic disorder that progresses gradually and silently for decades, experimental models reproduce an accelerated form of the disease that is not fully representative of this condition. Since human surgical specimens are scarce, experimental data are valuable but we must be aware of the drawbacks of experimental approaches [277]. In this context, there is an active search and progress in the development of preclinical models for this disease in order to improve their translational relevance. Further, approaching pharmacological studies in (i) aged animals, (ii) more than one experimental model representing distinct mechanisms of AAA and (iii) in the presence of comorbidities would increase the pathophysiological significance of the results. Of note, very few studies have addressed the impact of therapeutic strategies limiting the growth of already established aneurysms; in fact, the low number of AAA patients suitable for clinical trials enrolment remains one of the main obstacles to explore the effectiveness of any therapeutic strategy. Hence, to draw appropriate conclusions with translational value, the design of future preclinical investigations addressing novel medical therapies in AAA should consider all these aspects.

Data Availability

Not applicable.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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CRediT Author Contribution

Lídia Puertas-Umbert: Writing—original draft, Writing—review & editing. **Rafael Almendra-Pegueros:** Writing—original draft, Writing—review & editing. **Francesc Jiménez-Altayó:** Writing—original draft, Writing—review & editing. **Marc Sirvent:** Writing—original draft, Writing—review & editing. **María Galán:** Writing—original draft, Writing—review & editing. **José Martínez-González:** Conceptualization, Resources, Funding acquisition, Writing—original draft, Writing—review & editing. **Cristina Rodríguez:** Conceptualization, Resources, Funding acquisition, Writing—original draft, Writing—review & editing.

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Clinical Science (2023) **137** 1167–1194
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Abbreviations

AAA, abdominal aortic aneurysm; AMPT, α-methyl-p-tyrosine; ATF6, activating transcription factor 6; BET, bromodomain extra-terminal; ECM, extracellular matrix; ER, endoplasmic reticulum; MMP, metalloproteinase; NFB, nuclear factor kappa B; NOX, NADPH oxidase; PDE4, phosphodiesterase 4; ROS, reactive oxygen species; TH, tyrosine hydroxylase; VSMC, vascular smooth muscle cell; XBP-1, X-binding protein 1.

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Clinical Science (2023) **137** 1167–1194
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