Review

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Pathophysiological Aspects of The Development of Abdominal Aortic Aneurysm with a Special Focus on Mitochondrial Dysfunction and Genetic Associations

Abstract: Abdominal aortic aneurysm (AAA) is a complex degenerative vascular disease, with considerable morbidity and mortality rates among the elderly population. The mortality of AAA is related to aneurysm expansion (the enlargement of the aortic diameter up to 30 mm and above) and the subsequent rupture. The pathogenesis of AAA involves several biological processes, including aortic mural inflammation, oxidative stress, vascular smooth muscle cell apoptosis, elastin depletion, and degradation of the extracellular matrix. Mitochondrial dysfunction was also found to be associated with AAA formation. The evidence accumulated to date supports a close relationship between environmental and genetic factors in AAA initiation and progression. However, a comprehensive pathophysiological understanding of AAA formation remains incomplete. The open surgical repair of AAA is the only therapeutic option currently available, while a specific pharmacotherapy is still awaited. Therefore, there is a great need to clarify pathophysiological cellular and molecular mechanisms underlying AAA formation that would help to develop effective pharmacological therapies. In this review, pathophysiological aspects of AAA development with a special focus on mitochondrial dysfunction and genetic associations were discussed.

Keywords: abdominal aortic aneurysm; inflammation; mitochondrial dysfunction; genetic susceptibility; mitochondrial DNA.

Introduction

Abdominal aortic aneurysm (AAA) is associated with substantial morbidity and mortality worldwide, predominantly affecting older men aged 65 years and over [1-3]. Although women represent an increasing proportion (almost one-third) of the patients presenting to hospital with AAA rupture thus, they contribute to an increasing number of AAA-related deaths [4, 5]. Aortic aneurysm rupture causes profound internal bleeding and is usually lethal unless the repair is performed promptly. The mortality of ruptured AAA is over 80% [1].

It is considered that AAA is a permanent and irreversible dilatation in the infra-renal part of the aorta; the enlargement of the aortic diameter up to 30 mm and above. The natural course of AAA, the gradual expansion to ultimate rupture, significantly varies among individuals. Progressive AAA is typically asymptomatic until the rupture [6]. The standard of care for patients with large (≥55 mm in diameter), rapidly growing (>10 mm per year), and/or symptomatic AAAs is endovascular exclusion or open surgical repair, and these are the

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only therapeutic options currently available [7]. As for small AAAs (<55mm in diameter), surgical repair is not beneficial and therefore limited to regular imaging surveillance. A large randomized controlled clinical trial showed that survival rates were not increased after immediate elective repair of AAAs less than 5.5 cm in diameter [8]. Ultrasound-based screening aiming at those at risk (commonly men of 65-years and over) proven to be effective in reducing the risk of AAA-related mortality [9]. However, ultrasound screening does not provide possibilities to identify patients of high- or low risk for the disease progression. Therefore, there is an unmet clinical requirement to develop pharmacological or cell-based therapies that would restrict or prevent AAA formation, its progressive expansion, and rupture. The deficit in effective risk stratification strategies and of specific drug therapy drives significant interest in the pathogenesis of this condition. Even though the pathophysiological pathways underlying AAA have been broadly studied, a detailed pathophysiological understanding of AAA remains incomplete. In this review, we will discuss pathophysiological aspects of AAA development with a special focus on mitochondrial dysfunction and genetic associations.

Biological Processes Involved in AAA Formation

The pathophysiology of AAA is complex and associated with the degradation of the elastic media of the aortic wall, which leads to aortic dilatation and consecutive rupture. Numerous studies have been conducted on the molecular mechanisms implicated in AAA pathogenesis [10-12]. The following biological processes play a significant role in the development of this disorder: (i) chronic inflammation, (ii) degeneration and apoptosis of vascular smooth muscle cells (VSMCs), (iii) extracellular matrix (ECM) proteolysis, (iv) oxidative stress, (v) endothelial cell alteration, and (vi) formation of intraluminal thrombus. All these processes were described in detail by Golledge et. al. [13]. A large amount of evidence indicated the presence of innate and adaptive immune systems in AAA pathogenesis [12, 14-16].

Vascular inflammation is the major pathophysiological feature of the aortic aneurysm developmental process [13]. Multiple exogenous immune cells, such as lymphocytes, macrophages, mast cells, neutrophils, and natural killer (NK) cells, gradually infiltrate into the outer part of the aorta and often into surrounding tissue, thus, inducing the inflammatory response. The functional attributes of different populations of inflammatory cells in AAA tissue are unclear, but some evidence emerged indicating the role of T-cells and NK cells in the pathogenesis of AAA. It was demonstrated that T-cells can secrete proinflammatory cytokines [17] and NK cells have exhibited increased cytotoxicity that is a contributing factor in the generation or potentiation of inflammation in patients with AAA [18]. The infiltration of inflammatory cells promotes SMC production and activation leading to a secretion of several matrix metalloproteinases (MMPs), which are considered to be crucial enzymes causally linked to AAA formation and progression [19]. In particular, some studies support MMP2 and MMP9 as potentially important factors [20, 21]. These MMPs destroy and destabilize the mechanical property of the aortic wall by modulating interstitial elastin and collagen that results in the apoptotic loss of medial SMCs and ECM destruction, thus, promoting dilation and rupture of AAA. Interestingly, there is evidence suggesting that the chronic inflammation seen in AAAs is a result of a disturbed autoimmune response against autologous components of the aortic wall [22]. Moreover, new vessel formation (angiogenesis) was demonstrated within the adventitia of human AAA biopsies and implicated in promoting the influx of inflammatory cells [23]. Additionally, a number of inflammatory genes were found to be up-regulated in AAA murine models [24] and that supports the inflammation-mediated concept of AAA further.

Furthermore, many studies showed that promoting inflammation oxidative stress is a great contributor to AAA pathogenesis [25-27]. Human and animal studies suggested that oxidative stress is implicated in the vascular degeneration seen in AAA [28, 29]. The evidence coupling up oxidative stress with the increased matrix proteolysis, SMC apoptosis, altering mechanical forces, and further augmenting the cycle of inflammation was extensively reviewed [30]. The association of inflammatory cells with the elastic lamina disruptions and the presence of ROS is indicative that the natural course of AAA is a slow process, which eventually reaches a stress point resulting in the rupture of the aneurysm [31, 32]. Oxidative stress is excessive ROS production that prevails over antioxidant protection. In particular, overproduction of ROS occurs as a result of the imbalance between the activity of endogenous pro-oxidative enzymes (NADPH oxidase (NOX), xanthine oxidase (XO), and the mitochondrial respiratory chain) and the antioxidant enzymes (glutathione peroxidase (GP), haem oxygenase (HO), superoxide dismutase (SOD), thioredoxin (TRX), and catalase) [33, 34].

An important factor, which is also involved in AAA pathogenesis is alterations in the activity of the

renin-angiotensin system signaling pathway [35]. The impacts of angiotensin II on vascular cells have been extensively studied [23, 36, 37] and include several cellular mechanisms, such as generation of ROS, stimulation of MMPs, and infiltration of inflammatory cells. Interestingly, angiotensin II can mediate mitochondrial dysfunction in vascular endothelial cells [38, 39]. As for the molecular mechanism by which angiotensin II can generate an increased production of mitochondrial ROS, the involvement of NADPH oxidase-derived cytosolic ROS was shown [40]. Moreover, angiotensin II was demonstrated to inhibit mitochondrial sirtuin 3 and SOD2 through S-glutathionylation and acetylation, respectively, thus increasing mitochondrial ROS production [41]. Noteworthy, ROS generated by dysfunctional mitochondria can initiate an inflammatory response via the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway activation, which serves as a pivotal mediator of innate and adaptive inflammatory responses [42, 43]. It was also demonstrated that angiotensin II can regulate the morphology of mitochondria. The stimulation of angiotensin II caused mitochondrial fission, which was associated with dynamin-related protein-1 Drp1 Ser^{616} phosphorylation in VSMC culture [44]. Mitochondrial fission and fusion are regulated by several different proteins of which GTPases, Drp1 and mitochondrial fusion 1/2 proteins are key mediators of fission and fusion [45]. The association of mitochondrial dysfunction with the formation of AAA will be discussed further in the next section.

In addition, it is commonly believed that AAA development is associated with atherosclerosis [31, 46]. The investigation of human AAA biopsies has consistently found concurrent intimal atherosclerosis and most AAAs were considered to be caused by atherosclerosis [47]. Along these lines, atherosclerosis is an essential independent risk factor for AAA, as patients with AAA often have atherosclerosis. However, it is still not fully understood whether this alliance is contributory or a result of frequently shared risk profiles. Investigated AAAs have common risk factors with atherosclerosis, such as smoking, hypertension, and male gender [47, 48]. Some authors suggested that these pathologies are more discrete than commonly thought, pointing out the controversial role of atherosclerosis in AAA [25]. There is a large amount of evidence indicating that known high-risk factors for atherosclerosis, such as diabetes mellitus, hypercholesterolemia, and obesity, are less prominent in AAA; whereas, smoking, male gender, and ethnicity are particularly important in AAA development but less pronounced for atherosclerosis [47, 49-51]. Hypertension was found to have only a weak

association with AAA [50]. Remarkably, out of the risk factors known to be linked to AAA presence, only smoking and diabetes mellitus were revealed to predict AAA progression [50]. Importantly, the understanding of the atherosclerosis significance in AAA can be of therapeutic relevance. Human studies presented conflicting evidence on whether statins or angiotensin-converting enzyme inhibitors, which are effective in atherosclerosis, can also prevent AAA progression [52, 53, 54].

The biological processes involved in AAA formation are summarized in **Figure 1**.

Mitochondrial Dysfunction as an Important Contributor to the Formation of AAA

In general, the impairment of mitochondrial function is significant in the progression of ageing and age-related disorders [55]. Reduced mitochondrial respiration, as a result of mitochondrial dysfunctions, can manifest itself both in normal ageing of blood vessels and in age-related cardiovascular diseases including, atherosclerosis and the formation of the aneurysm [56]. There is a growing body of evidence indicating that disturbed mitochondrial functions are associated with AAA in both animal models and humans. These alterations include not only increased mitochondrial ROS production [57] but also dysregulation of mitochondrial biogenesis [47, 58] and mitochondria-dependent cellular apoptosis of aortic SMCs [59]. The oxidative damage of mitochondrial DNA (mtDNA) induces respiratory chain dysfunction via disruption of oxidative phosphorylation leading to reduced adenosine triphosphate (ATP) production, the molecular unit carrying intracellular energy, and further increased generation of ROS. Considerable data is indicating a decline in oxidative phosphorylation capacity of human mitochondria with age. Thus, mitochondrial dysfunction leading to the impaired mitochondrial respiration was found to be associated with age-related pathological changes, including both atherosclerosis and AAA formation. For instance, significantly reduced copy number of mtDNA, mitochondrial respiration, and the expression of specific electron transport chain complexes was demonstrated in VSMCs obtained from human atherosclerotic plaques [60, 61]. The differential expression of several genes related to mitochondrial function and oxidative phosphorylation was shown to be involved in AAA pathogenesis [62].

Evidence has emerged that the maintenance of mitochondrial homeostasis advocates mechanisms
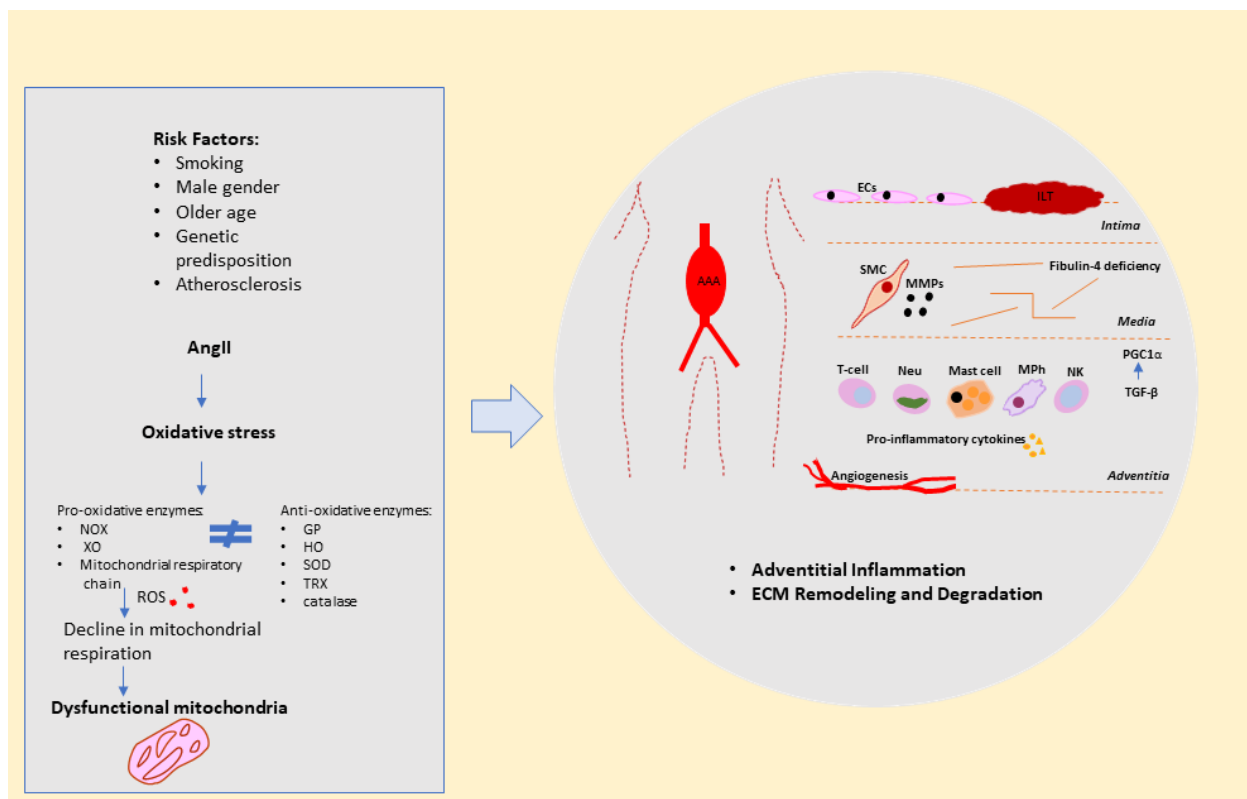
Figure 1: Schematic representation of biological processes involved in AAA formation.

Abbreviations: AAA, abdominal aortic aneurysm; AngII, angiotensin II; EC, endothelial cells; ECM, extracellular matrix; GP, glutathione peroxidase; HO, haemoxygenase; ILT, intraluminal thrombus; MMPs, matrix metalloproteinases; MPh, macrophage; Neu, neutrophil; NK, natural killer cell; NOX, NADPH oxidase; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; RAS, renin-angiotensin system; ROS, reactive oxygen species; SMC, smooth muscle cell; SOD, superoxide dismutase; TGF-β, transforming growth factor beta; TRX, thioredoxin; XO, xanthine oxidase.

involving mitochondrial dynamics or mitochondrial quality control that also participate in fundamental processes including ageing and AAA. The mitochondrial dynamics comprises of the following events: mitochondrial movement along the cytoskeleton, the regulation of mitochondrial architecture, and connectivity mediated by continuous fusion/fission [63]. Fission is involved in the selection of dysfunctional mitochondria; therefore, it is important for maintaining mitochondrial quality and integrity. Reduced mitochondrial fusion leads to loss of mtDNA and, as a consequence, to respiration deficient mitochondria [64]. In turn, respiration deficient mitochondria are selectively removed by mitophagy, an autophagy-lysosome system that degrades dysfunctional mitochondria by lysosome fusion [65]. Thus, consistent fusion and fission play a vital role in mitochondrial homeostasis and energy adaptation. It was demonstrated that inefficient fission and fusion contribute to ageing [66]. Besides, mitochondrial fission is involved in the

development of AAA, as suggested by recent data [67]. Moreover, mitochondrial mitophagy was observed to decline in ageing [68], as well as to be linked to the development of human AAA [69]. Inefficient removal of damaged mitochondria can lead to the excessive activation of inflammatory signaling pathways and subsequently to chronic systemic inflammation [70, 71]. In this way, in response to damaging stimuli, such as infectious pathogens and cellular debris, severe mitochondrial dysfunction mediates NLRP3 inflammasome hyperstimulation and mitochondrial ROS production causing caspase-1 activation. The presence of various identifiable causative pathogens, including *Staphylococcus, Streptococcus, Salmonella, Escherichia coli, Chlamydia* subspecies, *Cytomegalovirus* and other microorganisms was reported in AAA patients [72-75]. Activated caspase-1 generates mature pro-inflammatory interleukin (IL)-1β and IL-18 promoting inflammatory cell death and chronic inflammation associated with ageing

and age-related diseases [76]. Notably, the inflammasome activation leads to caspase-1-dependent mitochondrial damage and inhibits mitophagy [77]. Therefore, the appropriate mitochondrial functioning plays a crucial role in the innate immune system signal transduction with mitophagy as a key regulatory mechanism that maintains tissue homeostasis by limiting excessive inflammation. Innate immunity is involved in AAA progression [12]. Moreover, according to the oxy-"inflammaging" theory, oxidative stress impairs proinflammatory processes contributing to the further progression of various age-related diseases [78]. Excessive production of mitochondrial ROS, as a result of mitochondrial dysfunction, is a critical factor in the manifestation of "inflammaging", the chronic inflammation profile accompanying ageing [79]. The accumulation of damaged macromolecules during ageing by both, the increased production of ROS and/or by inadequate elimination due to mitophagy/autophagy decline are at least partially responsible for this chronic inflammation profile [79] [80]. In support of "inflammaging" being implicated in AAA, a large population-based study has found a strong positive relationship between AAA clinical incidence and circulating biomarkers of inflammation (C-reactive protein, white cell count, and fibrinogen) [81].

Several independent research groups have examined the relationship between mitophagy and mitochondrial mutations. The causative role of m.12338T>C mutation in decreased mitophagy was exhibited by decreased levels of autophagy protein light chain 3 and deposition of autophagic substrate p62 in the mutant cybrid cells as compared with control cell lines. These data established the direct link between mitochondrial dysfunction caused by complex I mutation and mitophagy, which determines the critical function of mitochondrial dynamics [82]. Numerous studies observed ageing-related accumulation of mtDNA mutations [83-86]. The accumulation of mtDNA mutations causing a decline in mitochondrial integrity and function is implicated in the cellular dysfunction associated with ageing and age-related pathology. The development of cytoplasmic cybrid cell line models made it possible to study the functional significance of mtDNA mutations. Using cybrids carrying point mutations in mtDNA, the significant accumulation of heteroplasmic mtDNA mutations in ageing mitochondria was demonstrated [87]. The results obtained in this study showed that ageing-related mtDNA mutations caused mitochondrial dysfunction by altering the oxidative phosphorylation machinery. These findings were consistent with previously reviewed data demonstrating that altering the expression of oxidative

phosphorylation complexes, mutations in mtDNA can lead to mitochondrial dysfunction and enhanced production of ROS [88]. Furthermore, if high levels of mtDNA mutations can lead to mitochondrial dysfunction, the impact that mtDNA mutations can have on a cell would be to impair its function ultimately leading to death. For instance, the respiratory chain deficiency triggered by the reduced mtDNA expression was shown to be associated with increased apoptosis in TFAM (nuclear-encoded mitochondrial transcription factor) knockout animal models [89]. The cellular damage and apoptosis-related to incorrect functioning of the respiratory chain and energy production caused by mutations in the mitochondrial genome are tightly implicated in AAA development [90]. It should be noted that, in most cases, mtDNA mutations are not specifically linked to certain pathological conditions. Mitochondrial mutations associated with cardiovascular diseases, such as atherosclerosis [91], type 2 diabetes [92], and acute myocardial infarction [93] were identified. Therefore, mitochondrial dysfunction may manifest itself in different pathologies, AAA including.

Mitochondrial DNA typically has higher mutation rates compared to nuclear DNA, as a result of its proximity to the site of ROS production, the deficiency of protective histone proteins, and the lack of a comprehensive DNA repair system [94]. Mutations of mtDNA are inherited by the maternal line and then reproduced by dividing mitochondria encompassing mutant mtDNA. This determines the high mutability rates of mtDNA, as well as the lifelong accumulation of somatic mutations of mtDNA [84, 86]. In each cell there is a high copy number of mtDNA which can exist in heteroplasmy containing both wild type and mutant mtDNA, or in homoplasmy containing identical mtDNA. In general, pathogenic mtDNA mutations are heteroplasmic [95]. MtDNA mutations could be caused by either replication errors or increased ROS production and, if a mutated mtDNA molecule undergoes subsequent replication and clonal expansion within a cell, this cell may become respiratory chain deficient [86, 96]. It is worth mentioning that the relationship between mtDNA mutations and oxidative stress in ageing and age-related diseases were extensively studied over several decades. The widely accepted mitochondrial free radical theory of ageing, which remained to be the predominant hypotheses in the field for many years, assumed the presence of a positive feedback loop (a "vicious cycle"). MtDNA accumulates genetic damage caused by the production of ROS during cellular respiration, in turn, dysfunctional mitochondria leak free radicals into the cytosol creating more mtDNA mutations [97]. However, some contradictory evidence on this theory emerged in

the past decade. A study suggested some factors that are mainly responsible for the majority of point mutations accumulating in mtDNA, including replication errors by DNA polymerase γ and/or spontaneous base hydrolysis [98]. Other experimental studies harbouring conflicting evidence on oxidative damage of mtDNA as a major driver of ageing were discussed in several reviews [99, 100]. Taken together, the impaired mitochondrial function due to oxidative damage of mtDNA, dysregulated mitochondrial biogenesis and dynamics can lead to disruption in the cell homeostasis, development of inflammation, excess of ROS, and loss of VSMCs, the hallmark pathophysiological processes of AAAs. Presented in this section, the information on mitochondrial dysfunction implicated in the AAA pathogenesis may appear to be rather speculative but it is hoped that it will encourage further investigation of this issue.

Mitochondrial Dysfunction-Associated Potential Molecular Mechanisms Underlying Aortic Aneurysm Formation

Several lines of evidence suggest an important role for Fibulin-4 deficiency associated with the formation of the aortic aneurysm [101, 102]. Fibulin-4 is a glycoprotein located in microfibril bundles and known to play a significant role in the formation of elastic fibres and maintenance of arterial wall integrity [103]. In an attempt to provide a comprehensive understanding of the molecular mechanisms underlying aortic aneurysm formation, a recent study by van der Pluijm et. al. has demonstrated a potential pathway linking the decreased expression levels of Fibulin-4 with ROS mitochondrial dysfunction, disturbed transforming growth factor-beta (TGFβ) signaling, and the dysregulated activity of peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC1α) [104]. This study used a combination of proteomics, genomics, and verifying functional experiments on thoracic aortas of aneurysmal mice with a four-fold reduction in the expression of Fibulin-4. The defective mitochondrial function, i.e., decreased mitochondrial respiration, as well as altered energy metabolism in aortic SMCs, were observed. It was found that Fibulin-4-deficient mice had increased TGFβ signaling. This was also confirmed by another study, in which the reduced levels of Fibulin-4 resulted in the increased TGFβ activation [105]. However, the mechanism by which Fibulin-4 deficiency

induces excessive TGFβ signaling remains unknown. Moreover, the increased TGFβ signaling decreased PGC1α transcriptional levels in Fibulin-4-deficient VSMCs and that is indicative that the increased TGFβ signaling is responsible for the decreased PGC1α expression levels in Fibulin-4-deficient aortas and VSMCs, hence, making an impact on mitochondrial respiration [104]. PGC1α is a transcriptional co-activator, which is expressed in tissues with high oxidative potential regulating mitochondrial function and energy metabolism in cells [106]. Of note, TGFβ signaling negatively regulating PGC1α expression levels was previously reported [107, 108]. It was also established that reduced PGC1α levels are involved in the reduced cellular metabolism and mitochondrial function [109]. PGC1α is engaged in fatty acid mitochondrial oxidation for energy in the cell via direct co-activation of the peroxisome proliferator-activated receptors (PPARs [α, β, and γ]), the major regulators of the cellular metabolic process [106]. PPARα and PPARγ play a central role in regulating the expression of proteins involved in extra- and intra-mitochondrial transport of fatty acids and oxidation. While PPARβ regulates the antioxidant synthesis, so that their reduced expression and activity may increase further ROS production. In this respect, the increased levels of ROS were observed in aneurysmal aortas of Fibulin-4-deficient mice [104]. Decreased expression of PGC1α protein was seen in patients with AAA indicating that PGC1α expression may play a regulatory role in both thoracic and abdominal aneurysms of the aorta [110]. In addition, improving mitochondrial function via PGC1α activation exhibited a favorable effect on ageing and longevity [111, 112].

Furthermore, in the study of van der Pluijm et. al., consistent with the reduced mitochondrial respiration, VSMCs derived from Fibulin-4-deficient mice exhibited reduced uncoupled oxygen utilization and increased acidification rates that may be indicative of the increased glycolysis. While PGC1α activation increased both basal and maximum oxygen utilization in VSMCs of Fibulin-4-deficient mice and improved cell proliferation proposing that the reduced proliferation phenotype can possibly be provoked by the increased TGFβ levels through a reduction in PGC1α levels. Similarly, another study reported that the lowering of TGFβ levels in Fibulin-4-deficient VSMCs amended their reduced proliferation rate [113]. In addition, the disruption of TGFβ signaling can attenuate proliferation and apoptosis of VSMCs and AAA formation [114]. Thus, the evidence presented above showed that Fibulin-4 deficiency can lead to the increased TGFβ1 signaling, which can cause not only alterations in protein composition affecting mainly ECM

and cytoskeleton proteins but also mitochondrial proteins (although mitochondrial structure and appearance remained unaffected, altered mitochondrial function and a reduction in mitochondrial size were observed) [104]. That may help to explain reduced mitochondrial respiration found in cells derived from different aneurysm phenotypes that also display increased TGFβ signaling, including Loeys-Dietz Syndrome, Arterial Tortuosity Syndrome, and Marfan Syndrome [102]. However, the exact mechanisms by which a deficiency in a protein involved in ECM structural integrity can lead to altered mitochondrial function and metabolism need to be elucidated. Finding mutual causal pathways with other TGFβ-linked vasculopathies may offer new options for preventative and therapeutic strategies for AAA.

Relying on studies demonstrating that TGFβ signaling negatively regulates PGC1α levels in several human aneurysm syndromes [107, 108], some authors suggest that this may be due to mitochondrial structural abnormalities [115]. However, a decrease in the copy number of mtDNA, mitochondrial respiration, and expression of PGC1α and several other regulatory genes of mtDNA synthesis was also observed in arterial ageing associated with ROS and loss and/or senescence of VSMCs [56]. In agreement with this study, an intriguing point of view was expressed that the changes seen in *Fibulin-4* deficient mice may have occurred as a result of VSMC loss and/or senescence in the arterial wall accompanied by the distorted mitochondrial function and increased generation of ROS [115].

Genetic Associations for AAA

Population-based studies have established that a combination of environmental and genetic factors which included smoking, older age, male sex, white ethnicity, and a family history of AAA determine the risk of developing AAA [47, 116]. Moreover, the robust evidence suggests that genetic variations contribute to the formation of AAA.

DNA Linkage Studies of AAA

It was estimated that heritability of around 70% is an important contributor to the overall AAA susceptibility [117] and that is indicative that genetic factors play a major role in the initiation and progression of AAA. The high prevalence of AAA was found among brothers supporting the contribution of genetic factor to AAA pathogenesis [118]. This study also established that the familial AAA cases were more likely to have AAA rupture compared

with the sporadic cases. Some studies on families, in which at least two relatives had AAA, revealed that the risk for developing an AAA is eight-fold higher for a first-degree relative than among the general population [119]. Family-based DNA linkage studies have provided unbiased means of identifying genetic risk factors for AAA [120, 121]. Using the affected-relative-pair approach, these studies discovered two genetic loci located on chromosomes 4q31 and 19q13 containing several plausible and physiologically relevant candidate genes, such as low-density lipoprotein receptor-related protein 3 (*LRP3*), peptidase D (*PEPD*), hepsin (*HPN*), interleukin 15 (*IL-15*), *GRB2*-associated binding protein 1 (*GAB1*), an endothelin receptor type A (*EDNRA*), thus providing the evidence for genetic heterogeneity and the presence of susceptibility loci for AAA. These genomic regions were assigned as AAA susceptibility loci in Online Mendelian Inheritance in Man (OMIM).

GWASs of AAA

According to current consensus, in some cases, the clinical phenotype, to a large extent, can be determined by the presence of a single nucleotide substitute in the nuclear genome. Nevertheless, it is usually difficult to establish a causal relationship between a particular variant of the nuclear genome and its corresponding phenotypic manifestation, therefore, identifying genetic predisposition to chronic pathologies, AAA including, can be challenging. Using single SNPs in AAA-relevant genes, almost 100 genetic associations have been reported [122]. In the past decade, the genome-wide associations study (GWAS) approach emerged as a targeted search for associations between single nucleotide polymorphisms (SNPs) and phenotypic traits of major human diseases, including AAA. A recent meta-analysis of GWASs has identified four novel SNPs specifically associated with AAA, such as 1q32.3 (SMYD2), 13q12.11 (LINC00540), 20q13.12 (near PCIF1/MMP9/ZNF335), and 21q22.2 (ERG) [123]. These associations were in agreement with known AAA biological pathways, implicating lipoprotein metabolism, inflammation, and ECM degradation but other potential pathomechanisms relating to transcription factor ERG and fibroblast growth factor 9 (FGF9) were also identified. The latter has a wide range of mitogenic and cell survival activities in VSMCs [124]. Besides, the latest GWAS study identified 14 novel loci of AAA risk variants, bringing the total number of known significant AAA loci to 24 [125]. Moreover, relying on the fact that some genetic and environmental risk factors are related to both

Table 1: The summary of several SNPs and their respective genes studied for conferring susceptibility to AAA.

SNP ID	Gene/Locus	Biological pathway involved	References
rs1626340 rs1036095 rs4522809	*TGFBR1* and *TGFBR2*	Vascular remodeling	[129]
rs7025486	*DAB2*IP	Cell growth and survival Lipid metabolism	[130]
rs7635818	*CNTN3*	Cell adhesion	[131]
rs3025058 rs2252070	*MMP3* and *MMP13*	Extracellular matrix	[132]
rs1800896	*IL-10*	Inflammation	[133]
rs10757278-G	*CDKN2BAS1* (*ANRIL*)	Inflammation	[134]
rs1466535	*LRP1*	Lipid metabolism	[135, 136]
rs1795061	*SMYD2*	Vascular development and EC/SMC differentiation	[123]
rs599839	*SORT1*	Altering circulating lipoprotein profiles	[137]
rs6511720	*LDLR*	LDL-cholesterol homeostasis	[138]
rs5186	*AGTR1a*	Renin-angiotensin system	[139]
rs4646994	*ACE*	Renin-angiotensin system	[140]

Note: all mutations had a significant association with an increased risk of AAA and can be found in a single nucleotide polymorphism database (www.ncbi.nlm.nih.gov/projects/SNP). *ACE,* angiotensin-converting enzyme; *AGTR1a*, angiotensin-renin receptor 1 alpha; *CDKN2BAS1*, antisense *RNA 1* gene; *CNTN3*, contactin-3; *DAB2IP*, GTPase activating protein; EC, endothelial cell; IL-10, interleukin 10; *LDLR*, low-density lipoprotein receptor; *LRP1*, low-density lipoprotein receptor-related protein 1 gene; MMP, matrix metalloproteinase; *SMYD2*, histone methyltransferase; *SORT1*, sortilin-1.

atherosclerosis and AAA, the gene regulatory function of rs2836411, the non-coding SNP located in an intron of the ERG gene, attracted special attention in a recent study [126]. It was found that ERG expression is likely to be affected by rs2836411 by altering both enhancer activity and local chromatin interactions. In atherosclerosis, the ERG gene is involved in vascular development, angiogenesis, and inflammation, hence, modulating ERG expression levels mechanistically, rs2836411 could also contribute to AAA pathogenesis. ERG is a transcription factor expressed in both hematopoietic and endothelial cells and mediates several key processes of vascular development, including endothelial specification, angiogenesis, and vessel stability [127]. An additional role of ERG in AAA formation is the observation that angiogenesis is increased in the aneurysm wall [128]. Previous GWASs also reported a substantial number of other significant AAA-associated SNPs and genes from genomic data. The summary of several SNPs and their respective genes studied for conferring susceptibility to AAA was presented in **Table 1.**

The information that was made available by GWAS of AAA outlines the role of common genetic variation in disease susceptibility. This can be helpful for the identification of the most promising molecular targets and candidate genes and their potential biological significance for further comprehensive research of AAA pathogenesis and therapy. Nevertheless, there are some limitations of GWAS that should be taken into account in order to place its results in the appropriate clinical context. First, one has to make sure that variants identified by GWAS are causal and it can take considerable effort to find functional SNPs. In fact, out of all GWAS-identified SNPs associated with AAA risk, only a limited number is actually causal. Second, GWAS fail to detect to what extent interactions between several variants or gene regions can affect the disease phenotype. Finally, GWAS has limited clinical predictive value and applicability. The latter is because of both the insignificant effect sizes and heritability of the majority of associations, which could be offset simply by environmental factors.

Concluding Remarks

With an ageing population, the prevalence of AAA may become more common in the future. In this review, we have attempted to define some of the important aspects that have emerged from the growing body of research on AAA pathogenesis. The development of AAA is a result of several factors, including a reduction in VSMCs, activation of MMPs, ECM disruption, and inflammatory cell infiltration. Moreover, several lines of evidence point toward mitochondrial dysfunction implicated in AAA development, hence, its role in AAA pathogenesis should not be underestimated. Potential mitochondrial dysfunction-associated molecular mechanisms underlying aortic aneurysm formation were described in this review. Besides, there has been a dramatic expansion in the research on genetic associations of AAA. Despite the considerable advances in the field, many uncertainties in mechanisms of AAA formation remain to be elucidated. The lack of understanding hinders the development of a comprehensive approach for better management of patients with AAAs in clinical settings.

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