Chapter

Pathogenesis of Abdominal Aortic Aneurysm

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Abstract

Abdominal aortic aneurysms (AAAs) are encountered by many healthcare providers such as interventional radiologists, vascular surgeons, cardiologists, and general practitioners. Much effort has been placed in the screening, diagnosis, and treatment of AAA with somewhat little understanding of its pathophysiology. AAA is a complex disease typically segmented into a process of proteolysis, inflammation, and vascular smooth muscle cell (VSMC) apoptosis with oxidative stress balancing its components. AAA and other aortic syndromes such as aortic dissection share this same process. On the other hand, AAA formation and aortic pathology may be acquired through infection like in mycotic aneurysm or may be genetic in origin such as seen with Ehlers-Danlos and Marfan syndromes.

Keywords: abdominal, aortic, aneurysm, dissection, mycotic, atherosclerosis, proteolysis, inflammation, oxidative stress, VSMC apoptosis, Marfan, Ehlers-Danlos, endovascular, vascular

1. Introduction and background of AAA

Abdominal aortic aneurysm (AAA) is a complex disease comprised of multifactorial molecular processes that carry a host of players yet to be solidified in literature. Although options continue to expand in the treatment of AAA, understanding the pathophysiology is pivotal for the development of screening tests and pharmacological treatment modalities.

In this chapter, we will go beyond the clinical context of AAA and discuss the various pathologic pathways that lead to its creation. Some of these pathways overlap with other aortic pathologies such as aortic dissection as well as mycotic aneurysm. Lastly, we will discuss common genetic disorders that are predisposed to aortic aneurysm and aortic dissection.

2. Abdominal aortic aneurysm

2.1 Normal anatomy and histology

The aorta is the main artery of the body that carries oxygenated blood from the heart to the remaining major arteries of the body. It may be segmented into the thoracic aorta and abdominal aorta based on its location to the diaphragmatic hiatus.

There are three sheaths that make up the aortic wall: tunica intima, tunica media, and tunica adventitia. The intimal layer is thin and mainly composed of endothelial cells, while the tunica media is the largest component of the aortic wall and consist of elastic fibers, smooth muscle cells, and collagenous tissue. Connective tissue makes up the most outer layer called the tunica adventitia and contains small blood vessels known as the vasa vasorum, which supply the cells of the arterial wall.

An aneurysm is defined as the localized dilatation of a vessel exceeding 1.5 times the normal diameter of the vessel, which is defined as greater than 3 cm in the abdominal aorta. As the abdominal aorta dilates, it becomes prone to rupture or tearing within the layers of its wall, otherwise known as aortic dissection (AD). In AAA and AD, patients may present with low blood pressure and a tearing sensation in the chest or back. When blood rushes into the medial layer forming a new, "false" lumen, further expansion can compress the "true" lumen causing downstream ischemia.

2.2 Role of aortic atherosclerosis

Atherosclerosis is often present in the setting of aortic pathology and although no causal pathway has been established, understanding the bridge between atherosclerosis and the inflammatory response in AAA remains essential. Early atherogenesis begins with subendothelial retention of circulating lipoproteins on proteoglycans within the extracellular matrix of the arterial wall. Aggregation and oxidation of retained lipoproteins further leads to a maladaptive immune response with circulating monocytes entering the subendothelium, differentiating into macrophages, ingesting the modified lipoproteins, and transforming into the classic "foam cell." The release of cytokines in this process, such as tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), leads to immune cell infiltration and inflammation [1, 2].

2.3 Pathogenesis of abdominal aortic aneurysm

Much of our understanding of AAA until this point arises from histopathological studies dating back to 1972 when the "Inflammatory" variant of AAA was described [3]. Since then, the most prevalent features of studied AAA segments have demonstrated elastin degeneration, immune cell infiltration, and apoptosis of vascular smooth muscle cells (VSMCs). Although the complete pathogenesis is unknown, information from animal models, histopathological studies and genome-wide association studies (GWAS) may be used to partition this intricate process into proteolysis, inflammation, and vascular smooth muscle cell (VSMC) apoptosis. Oxidative stress appears to be a major player as well and balances different facets of AAA development and growth.

2.3.1 Proteolysis

During aneurysmal growth, significant proteolytic degradation of elastin, collagen, laminin, fibronectin, and many other extracellular matrix (ECM) proteins occurs in the arterial wall. Upregulation of proteolytic enzymes in the aortic wall is stimulated by the presence of oxidized LDL and cytokines such as TNF-α, IL-1, and IL-3 [4]. The most famous set of proteolytic enzymes are known as the matrix metalloproteinases (MMPs), which have been implicated in cancer, wound healing, and many other processes. During normal homeostasis, regulation of MMPs in the aortic wall is carried out by tissue inhibitors of MMPs (TIMPs), but a higher MMP/TIMP ratio is typically observed in aneurysms [5, 6].

Of the multiple MMPs, MMP-9 and MMP-2 are considered crucial participants in AAA and aortic dissection (AD) development, both significantly upregulated in AAA segments with MMP-9 expression correlating with aneurysm diameter. MMP-9 is derived from macrophages and neutrophils and MMP-2 is produced by smooth muscle cells and fibroblasts; together, they both balance ECM remodeling, inflammation, and VSMC apoptosis through various signaling pathways such as the MAPK (mitogen-activated protein kinase)/ERK pathway [7]. TGF-beta signaling pathways help balance MMP-2 and MMP-9 in addition to creating protection against AAA formation by increasing type I and III collagen production and upregulating protease inhibitors [8].

2.3.2 Inflammation

Innate and adaptive arms of the immune system are involved in the development and growth of AAA. Neutrophil infiltration and release of elastase induces early degradation of the ECM in the aortic wall. Elastin breakdown products trigger either pro-inflammatory or anti-inflammatory macrophages in the adventitial layer of the aortic wall. T-cell derived interferon gamma and B cells are also involved in AAA formation. B cells provide a source of immunoglobulins, complement pathway, and cytokines, which add to the complexity of AAA formation [9–11].

2.3.3 VSMC apoptosis

Necrosis and apoptosis have traditionally been deemed different mechanisms [12]. Apoptosis is considered an organized and instructed route of cell death while necrosis is regarded as an unorganized disruption of a cell with an additional immune response. With this in mind, VSMC apoptosis occurring in the tunica media of the aortic wall in AAA formation is not a recent discovery, although the exact phenomenon is not known.

In addition to a review on cell death nomenclature, Wang et al. describe receptor-interacting protein kinase 3 (RIP3) on VSMCs as a key player in a structured form of necrosis, also known as necroptosis [12]. It is believed that RIP3 mediating inflammatory cytokine production by smooth muscle cells is mediated in the aortic wall through TNF-α signaling pathways. Additionally, protein kinase C-delta (PKC) is upregulated in aneurysmal tissues which lack VSMCs and murine models have demonstrated decreased RIP3 levels in aortic tissue that lacks PKC, further validating the role of PKC in AAA formation [13, 14].

2.4 Oxidative stress

2.4.1 Defining oxidative stress

Oxidative stress is defined as cellular injury induced by reactive oxygen species (ROS) and reactive nitrogen species (RNS), taken as a combined ROS/RNS system [15]. Pathologic oxidative stress to the vasculature occurs via a multi-faceted, highly complex mechanism that is thought to occur in part by the ROS/RNS system. The ROS/RNS system is defined as a group of molecules consisting of free radicals or molecules which predispose to free radical formation. A free radical is any species that contains one or more unpaired electrons that is capable of existing independently, which makes them highly unstable and will react readily with lipids, cellular proteins, and nucleic acids [15, 16].

2.4.2 Normal pathophysiology and regulation

The production of ROS/RNS is highly regulated and occurs naturally to some degree in all normal cells due to the incomplete reduction of molecular oxygen to water during cellular respiration and within phagosomes of phagocytic cells (chiefly neutrophils and macrophages) [15]. ROS/RNS are typically short-lived, owing to their instability and prompt removal/inactivation by endogenous cellular antioxidants and antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase. Dysregulation occurs when ROS/RNS production exceeds clearance.

2.4.3 The various ROS/RNS entities and their chemical reactions

The principal ROS/RNS involved in cellular injury include superoxide, hydrogen peroxide, hydroxyl radicals, and peroxynitrite. These entities mediate vascular damage either directly or indirectly by conversion to more reactive substances [15, 16].

a. *Hydrogen peroxide.* Hydrogen peroxide (H_2O_2) is the most abundant non-radical oxidant and is formed mostly from superoxide dismutase acting on superoxide radicals [16]. In and of itself it is stable in configuration, weakly oxidizing, and can cross cellular membranes. In the presence of transitional metallic elements such as iron (Fe), hydrogen peroxide can decompose into a highly reactive and unstable hydroxyl radical (OH) in a process known as the Fenton reaction. In the Fenton reaction, peroxide is removed via conversion to H_2O and O_2 via catalase and glutathione peroxidase. Furthermore, hydrogen peroxide can be broken down into far more reactive species. For example, hydrogen peroxide will react with NO to form peroxynitrite ($ONOO^-$), a potent mediator of vascular damage. Peroxynitrite causes inactivation of enzymes by oxidation and nitration, MMP induction with subsequent vascular connective tissue breakdown, and lipid peroxidation [15–17].

b. *NADPH oxidase*. NADPH oxidase, also known as "Phagocyte Oxidase," is a well-known enzyme encoded by the NOX gene family. The NOX family is made up of multiple protein subunits that collectively oxidize nicotaminide-adenine dinucleotide phosphate (NADPH) to reduce molecular dioxygen (O_2) into the superoxide anion ($O_2^{\bullet -}$) [15, 16]. In combination with myeloperoxidase and other enzymes, NADPH oxidase is required in the oxidative destruction of microbes via phagocytosis, classically known as the "respiratory burst." In comparison to the oxidative stress in AAA, the respiratory burst occurs within the contents of a phagolysosome, so the host cell contents are protected from the ROS that are generated. Since phagocytic cells such as macrophages are also strongly implicated in the inflammatory response associated with pathology of the aortic vessel wall, it follows that membrane-bound NADPH oxidase has been suggested as one of the predominant sources of vascular ROS linked to oxidative stress in aortic pathologies such as AAA and AD [18–20].

c. The hydroxyl radical is produced by a variety of chemical reactions involving H_2O_2, H_2O, and $O_2^{\bullet -}$. The hydroxyl radical is highly reactive and will readily react with virtually any biomolecule it encounters in a short diffusion distance (about the diameter of the typical protein) [16]. It is removed via conversion to H_2O via glutathione peroxidase and has direct damaging effects on lipoproteins and DNA.

2.4.4 Reactive nitrogen species

In addition to ROS, reactive nitrogen species (RNS) also play a role in the pathophysiology of vascular dysfunction. Nitric oxide (NO) is produced via an L-arginine precursor by nitric oxide synthases with multiple cofactors. Encoded isozymes of mammalian NOS include endothelial, neuronal, and inducible subtypes (eNOS, nNOS, and iNOS, respectively). Endothelial homeostasis rests firmly upon tight regulation of endogenous NO production, but pathologic uncoupling of NOS isozymes or IFN-γ mediated NO production by macrophages can lead to excess NO and/or ROS. Peroxynitrite ($ONOO^-$), a powerful non-radical nitrosative stressor, is formed by the reaction of $O_2^{\bullet-}$ and NO and serves as the basis for other RNS derivatives such as nitrogen dioxide (NO_2) [16, 17].

Peroxynitrite is a highly reactive proatherogenic mediator and readily reacts with protein side chains and carbon dioxide to cause cellular injury [16]. A notable example is 3-nitrotyrosine, formed by the reaction of peroxynitrite with tyrosine, which has been suggested as a local marker of oxidative stress in immunostained samples of aneurysmal aortas [19]. Additionally, Kotlarczyk et al. revealed a pathway consisting of oxidative and hemodynamic stress on the aortic wall leading to increased superoxide production and NO bioavailability. This linkage corresponded to an increased rate of asymmetric thoracic aorta dilatation in patients with bicuspid aortopathy versus their tricuspid counterparts [20].

2.4.5 Role of oxidative stress in aortic pathology

The role of oxidative stress in the pathogenesis of aortic pathologies such as aortic aneurysm involves pathologic vascular remodeling along with dysfunctional balancing of connective tissue breakdown and synthesis by VSMCs [19–21]. This is thought to occur due to several mechanisms, including ROS/RNS induced VSMC apoptosis and enhanced matrix metalloproteinase (MMP) activity, which leads to progressive weakening of the aortic wall, dilatation, and eventual aneurysm formation via the breakdown of collagen, elastin, and laminin. Oxidative stress is a major modulator of MMP formation and can disrupt the corresponding balance of TIMPs that are otherwise crucial to the structural integrity of the extracellular matrix of the arterial wall [21, 22].

Additionally, ROS can disrupt VSMC proliferation via a mechanism linked to the relative local redox microenvironment concentrations of hydrogen peroxide and lipid hydroperoxides [16, 18, 23]. Hydrogen peroxide is involved in various pathways and serves as a mediator of vascular inflammation, upregulating various chemotactic and adhesion molecules such as ICAM-1, IL-8, and P-selectin which facilitate leukocyte migration into the aortic wall. In a study of patients undergoing elective infrarenal AAA repair, tissue samples of aneurysmal aortic segments demonstrated superoxide levels 2.5 times that of adjacent non-aneurysmal aortic segments, as well as increased expression and activity of NADPH oxidase [18]. In addition, changes in normal local blood flow hemodynamics in aneurysmal aortas may also induce ROS production and contribute to aortic remodeling and dissection [20, 24, 25].

Xanthine oxidoreductase (XOR) is a famous complex molybdoflavin protein known to healthcare providers as a catalyzer in the terminal steps of purine degradation, and when therapeutically inhibited, a target for treatment of hyperuricemia and gout. Although XOR may be involved in the pro-inflammatory state associated with crystal formation in gout, it may have an antioxidant role when under the optimal conditions, which necessitates further studies [26].

2.5 Aortic dissection

Similar to AAA, the physiology of aortic dissection (AD) entails a complex multifactorial process consisting of proteolysis, inflammation, and VSMC apoptosis. The differentiating factor is that hemodynamic stress results in intimal tearing of the aortic wall allowing blood to rush into the medial layer. This process creates a "true" and "false" lumen that may propagate in either direction to occlude the true lumen and/or cause a variety of issues resulting in significant morbidity and mortality.

2.6 Mycotic aneurysm

A mycotic aortic aneurysm is characterized by a local, irreversible dilatation of the aorta which is secondary to a direct bacterial or fungal inoculation of the vessel wall. The term mycotic aneurysm is actually a misnomer, as these "infective" aneurysms are most commonly bacterial in nature and fungal to a lesser extent. Staphylococcus and Salmonella species are the two most commonly cultured organisms in mycotic aneurysms, however, improved bacteriologic techniques have led to the detection of anaerobic bacteria (mostly Bacteroides, and Clostridium spp.). Mycotic aneurysms are rare as they only represent 1–2.6% of all aortic aneurysms [27, 28].

The formation of mycotic aneurysms is initiated by a microbial induced pro-inflammatory cascade of cytokines, such as TNF-α, IL-1, IL-6, invading the aortic vessel wall [28]. The recruitment of inflammatory cells within the vessel causes functional changes to VSMCs and endothelial cells with subsequent loss of integrity in the tunica media. This intense cytokine cascade causes mycotic aneurysms to progress more rapidly and aggressively than inflammatory aneurysms and thus have a higher mortality rate when compared [29].

Mycotic aneurysms most commonly affect diseased aortic endothelium in the setting of bacteremia and may present as nonspecific back pain or abdominal pain depending on the location of the lesion. Patients will typically be febrile, indicating a systemic infection, and lab values will show signs of leukocytosis and elevated ESR. Importantly, Gram negative organisms tend to cause a more virulent arterial infection than Gram positive bacteria, which makes the resultant aneurysm even more prone to rupture and further increases the risk of mortality [30–32].

Treatment of mycotic aneurysm focuses on empiric antibiotic therapy while waiting for blood culture susceptibility panel with individualized duration, surgical excision with wide debridement of infected tissues, and revascularization as needed.

2.7 Screening and diagnosis of AAA

The primary role of AAA screening and surveillance is mortality reduction, primarily through one-time and/or periodic non-invasive imaging. The initial workup of any aortic pathology begins with a focused history and physical examination. Classically, AAA may present with a pulsatile epigastric abdominal mass, but many patients are asymptomatic and lack this finding. However, the physical exam may assist in identifying more distal aneurysmal disease, particularly those occurring in the femoropopliteal distribution, which may be predictive of coexisting AAA. The physical examination is also crucial to determine a patient's baseline status in terms of perioperative risk with regards to a future surgical or endovascular intervention [33]. A number of serum biomarkers and genetic factors are known to be associated with AAA, and despite being an exciting area of developing research, the prognostic and diagnostic value of these factors has not yet been validated clinically, and therefore do not yet play a significant role in the diagnosis and management of AAA [33].

2.7.1 Screening

Ultrasound (US) and computed tomography (CT) angiography are the two primary imaging modalities used for AAA and are both highly accurate and reproducible. Transabdominal US is relatively inexpensive and can be performed in minutes without the use of ionizing radiation or iodinated contrast media. US carries a sensitivity and specificity approaching 100% in asymptomatic patients with AAA, making it the modality of choice for AAA screening and surveillance. Both the Society for Vascular Surgery (SVS) and the US Preventive Services Task Force (USPSTF) recommend a one-time screening ultrasound for AAA in men or women 65–75 years of age with a history of tobacco use [33, 34]. Various additional recommendations exist for that of first-degree relatives of those presenting with AAA, follow-up US examinations based on initial aortic diameter at initial screening, and screening in non-smokers or females, but these recommendations are supported by lower-level data or are of unclear benefit. Obesity, overlying bowel gas, and user dependence are recognized limitations ultrasound evaluation for AAA, and US may underestimate AAA size by 2 mm [33, 34]. However, limitations are invariably offset by the aforementioned benefits, and US can be useful evaluating other causes of abdominal pain, particularly in the emergent setting, resulting in a reduction in time to diagnosis and treatment. When AAA repair is indicated in an otherwise stable patient, CT offers more precise pre-operative planning via multiplanar orthogonal measurements.

2.7.2 Surveillance

Aside from baseline screening, AAA surveillance also plays a significant role in mortality reduction, by monitoring changes in AAA size over time and subsequent timely identification of patients whose risk of rupture begins to approach or outweigh the risks of intervention. Despite multiple large-scale clinical research trials comparing AAA size versus risk of rupture, vascular and radiology literature has yet to produce a single unifying surveillance parameter, but several evidence-based criteria allow patients to be safely observed over time despite a relatively small background risk of rupture. The SVS recently provided updated guidelines for the surveillance of patients with AAA, including recommended surveillance imaging at 3-year intervals for patients with AAA between 3.0 and 3.9 cm in diameter, 12-month intervals for 4.0–4.9 cm, and 6-month intervals for 5.0 and 5.4 cm [33]. The American College of Radiology (ACR) appropriateness criteria designates duplex ultrasound of the aorta/abdomen, CTA of the abdomen and pelvis with intravenous contrast, or MRA of the abdomen and pelvis with intravenous contrast as "usually appropriate" (a rating of 7, 8, or 9) for surveillance of asymptomatic AAA without previous repair [35].

The remaining aortic pathologies, including that of aortic dissection, present with a wide range of clinical, laboratory, and imaging findings, and therefore are similarly evaluated with CT or CT angiography for prompt diagnosis.

2.8 Treatment of AAA

2.8.1 Medical therapy

Hypertensive disease is the main major risk factor for aortic thoracic disease with genetic predisposition as second major risk factor [36, 37]. Although, this notion is based on studies mostly including Marfan disease patients [38]. For patients with asymptomatic AA, anti-hypertensive therapy with beta blockers is

recommended for blood pressure control with the goal being to limit aortic wall expansion. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ARBs) are preferred as well due to their role as modifiers of inflammatory mediators and by decreasing vascular smooth muscle apoptosis [38, 39].

Beta blockers have been the traditional treatment for thoracic aortic disease. It was originally demonstrated more than 70 years ago when turkeys eating sweet pea seed, *Lathyrus odoratus*, which contains the lysis oxidase inhibitor, B-aminopropionitrile, die of acute aortic dissections. The beta blocker propranolol was found to decrease deaths from dissection in B-aminopropionitrile fed turkeys [40–43]. Beta-blockers such as propranolol benefit the aortic wall through negative inotropic and chronotropic effects. Through these effects, the elastic fibers of the wall are protected from further damage and is further supported by reduction in left ventricular pressure of the heart and heart rate [44]. However, the benefit of beta-adrenergic blockade is better established in aortic dissection than in AAA because beta blockers provide theoretical benefit on blood pressure and left ventricular pressure reduction [45].

Angiotensin converting enzyme inhibition may have a beneficial role by modifying inflammatory mediators and decreasing vascular smooth muscle apoptosis. Angiotensin receptor blockers such as Losartan have been shown to prevent expansion of aneurysms by downregulation of transforming growth factor B [38, 46, 47]. Angiotensin II type 1 receptor blockade within the renin-angiotensin-aldosterone system causes a decrease in TGF-B signaling further reducing levels of intracellular mediators within the TGF-B signaling cascade, such as phosphorylated SMAD [37, 48]. By this mechanism, there is a reduced proliferation of vascular smooth-muscle cells, fibrosis, and expression of matrix metalloproteinases [49]. Overactivation of the angiotensin II type 2 receptor pathway by ARBs causes antiproliferative and anti-inflammatory effects that are beneficial in aortic wall homeostasis [50]. In contrast, ACE inhibitors limit the production of angiotensin II, producing a negative effect on Angiotensin II type 1 and type 2 receptor pathways which do not influence alternative mechanisms [46].

Medical treatment with statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) power many of the inflammatory pathways of the formation of aortic aneurysms. Statins provide a protective effect by inhibition of matrix metalloproteinases (MMPs) and plasminogen activator due to the aforementioned proteolytic enzymes involved in the pathophysiology of aortic aneurysm formation [39, 51, 52].

2.8.2 Surgical and endovascular treatment

Historically, abdominal aortic aneurysm was treated with open surgical repair once aneurysmal growth reached a certain size or rate. Recent advancements have allowed endovascular repair to be used as the primary modality of repair with open surgical repair reserved for emergency/unconventional situations.

3. Genetic etiologies of aortic aneurysms and dissections

Genetics play an important role in the pathogenesis of various diseases. While multifactorial processes have been described in the development of AAA and AD, there are two Mendelian disorders which may lead to AAA or AD, Marfan syndrome and Ehlers-Danlos syndrome (EDS). Both have been connected to the development of AAs and ADs lacking classic risk factors such as smoking, hypertension, and old age. By definition, both of these syndromes result from mutations in a single gene

and inheritance pattern. Overall, both Marfan syndrome and EDS share deleterious effects on connective tissues in the body which consequently have major ramifications on the integrity of major blood vessels.

3.1 Ehlers-Danlos syndrome

Ehlers-Danlos syndromes (EDS) are a rare group of inherited disorders of collagen which ultimately impair the integrity of the extracellular matrix of supporting structures such as connective tissues. Clinically, people with EDS usually feature remarkable hyperelastic skin, hypermobile joints, and often a bleeding diathesis. At least six clinical and genetic variants of EDS have been established and they all share a generalized defect in collagen, including abnormalities in its structure, synthesis, secretion and degradation.

In this discussion, the vascular subtype of EDS, previously referred to as type IV EDS, is the focus of this section. The vascular subtype of EDS (vEDS) is manifested from a key mutation affecting the COL3A1 gene, which subsequently causes deficient synthesis of type III procollagen. The diagnosis of vEDS is made from major and minor clinical criteria and can be confirmed by abnormalities in procollagen production as seen in protein gel electrophoresis and molecular genetic testing.

3.1.1 Epidemiology of EDS

The incidence of vEDS is roughly 1:100,000 with a total of 1500 affected individuals in the United States having been identified on the basis of biochemical and genetic testing and analysis of family pedigrees [53].

3.1.2 Molecular genetics of EDS

The COL3A1 gene is found on chromosome locus 2q32.2 and encodes for type III pro-collagen. The COL3A1 is estimated to be over 44 kb in size [54]. The vEDS subtype is inherited in an autosomal dominant pattern.

3.1.3 Pathogenesis of EDS

Type III collagen is extremely prevalent in skin, vessel walls and reticular fibers of most tissues such as the lungs, liver, and spleen. Mutations in the COL3A1 gene responsible for vEDS can take various forms. These include point mutations, deletions, insertions, splicing mutations, and missense mutations. The most common genetic mutation associated with vEDS is a missense mutation of a crucial glycine residue in the triple helical domain of the alpha-1 (III)-chains of type III procollagen. The mutation almost always occurs in a particular region of the protein that is used to bind to other collagen proteins. Three collagen proteins always bind together into a trimer, which is required for collagen functionality; when not bound in a trimer, collagen is useless, as it cannot provide functional or structural support [55].

The most common missense mutation recognized in the literature is a substitution of glycine to glutamic acid or lysine (Glu>Lys), both leading to the production of a defective polypeptide and disrupted (Gly-X-Y)n collagen motif [56]. This leads to the development of severely malformed collagen fibrils and reticulin fibers in the extracellular matrix of dermal and arterial tissues.

Type III procollagen is a major structural protein in hollow organs and vessel walls. An altered structure of the protein makes it dysfunctional in large elastic arteries such as the aorta causing them to be more prone to rupture or dissection. The mechanisms by which mutant type III collagen molecules create vascular

fragility are not well understood in humans, though clinically vEDS is characterized by weakness of tissues rich in type III collagen, such as blood vessels, thus predisposing them to aneurysm and dissection [57].

3.2 Marfan syndrome

Marfan syndrome is caused by an inherited mutation of the FBN1 gene coding for the extracellular glycoprotein Fibrillin-1. The mutation in FBN1 initiates instability of connective tissue extracellular matrix, manifesting broadly as changes to the skeleton, eyes, and cardiovascular system. There have been more than 1800 distinct causative mutations in the FBN1 gene which complicates the diagnosis by DNA sequencing alone. As a result, the diagnosis of Marfan syndrome is mainly based on clinical findings. Classically you will see ectopia lentis, tall stature with coinciding arachnodactyly, and hyperlaxity of joints.

3.2.1 Epidemiology of Marfan syndrome

The prevalence of Marfan syndrome is estimated to be 1 in 5000. According to National Human Genome Research Institute, roughly 75% of cases are familial and the remaining 25% of cases are a result of a new (de novo) mutation in the FBN1 gene. In a 2015 study involving 412 people confirmed as having Marfan syndrome, the median age at diagnosis is found to be 19.0 years [58].

3.2.2 Molecular genetic of Marfan syndrome

Fibrillin-1 is encoded for by the FBN1 gene (chromosome locus 15q21) which is estimated to be 235 kb in size [59]. Marfan syndrome is inherited in an autosomal dominant pattern.

3.2.3 Pathogenesis of Marfan syndrome

Fibrillin-1 is secreted by fibroblasts, is modified post-translationally by glycosylation, and is the major component of microfibrils found in the extracellular matrix of connective tissue. Microfibrils are widely distributed in the body, more specifically they are abundant in the aorta, ligaments, and the ciliary zonules that support the ocular lens. This distribution of microfibrils gives rise to the unique clinical presentation classically known as Marfanoid habitus.

More recently, microfibril-associated glycoprotein 4 (MFAP4) has been linked to the pathogenesis of Marfan syndrome. Yin et al. using a glycoproteomic analysis of aortic extracellular matrix in Marfan patients, found an increased and more diverse N-glycosylation of MFAP4 in patients with Marfan syndrome compared with control patients. Most importantly in our discussion of AA and AD, this increased N-glycosylation was particularly in the aneurysmal stages [60, 61].

The defective Fibrillin-1 protein and subsequent faulty microfibrils are fundamental in the progression to an aortic aneurysm or an aortic dissection seen in Marfan syndrome. Not only do microfibrils provide structural integrity of specific organ systems, but they also provide a scaffold for elastogenesis in elastic tissues, most notably in elastic arteries such as the aorta [62]. In a way, malfunctioning FBN1 gene inserts malware into microfibrils, thus dismantling the scaffold needed for elastogenesis. This defective elasticity in the tunica media of elastic arteries such as the aorta weakens the vessel wall predisposing to early aneurysm. Weakening of the media also predisposes to any intimal tear, which may initiate an intramural hematoma that cleaves the layers of the media to produce aortic dissection.

Interestingly, the loss of microfibrils also gives rise to abnormal and excessive activation of transforming growth factor-B (TGF-B). Normally sequestered by well-functioning microfibrils, excessive TGF-B signaling has deleterious effects on both vascular smooth muscle development and the overall integrity of the extracellular matrix at a cellular level. Excessive TGF-B signaling in the adventitia of large elastic arteries causes increased deposition of weak fibrotic tissue leading to aneurysm development [58].

4. Conclusion

The pathogenesis of AAA formation is complex and multidimensional. The traditional atherosclerotic or inflammatory variant of AAA may be segmented into a process of proteolysis, inflammation, and VSMC apoptosis. Oxidative stress acts as a fulcrum throughout this process which is also involved in other acquired aortic pathologies such as mycotic aneurysm and aortic dissection. Classically, aortic pathology is affiliated with connective tissue disorders like seen in Marfan and Ehlers-Danlos syndromes. With further studies and eventual development, the understanding of AAA formation as well as other aortic pathologies will lead to additional treatment tools for vascular specialists and other healthcare providers alike.

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