REVIEW

The genetics and biomechanics of thoracic aortic diseases

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Abstract

Thoracic aortic aneurysms and aortic dissections (TAAD) are highly fatal emergencies within cardiothoracic surgery. With increasing age, thoracic aneurysms become more prevalent and pose an even greater threat when they develop into aortic dissections. Both diseases are multifactorial and are influenced by a multitude of physiological and biomechanical processes. Structural stability of aorta can be disrupted by genes, such as those for extracellular matrix and contractile protein, as well as telomere dysfunction, which leads to senescence of smooth muscle and endothelial cells. Biomechanical changes such as increased luminal pressure imposed by hypertension are also very prevalent and lead to structural instability. Furthermore, ageing is associated with a pro-inflammatory state that exacerbates degeneration of vessel wall, facilitating the development of both aortic aneurysms and aortic dissection. This literature review provides an overview of the aetiology and pathophysiology of both thoracic aneurysms and aortic dissections. With an improved understanding, new therapeutic targets may eventually be identified to facilitate treatment and prevention of these diseases.

Key Words

- thoracic aorta
- biomechanic
- aorta
- dissection
- aneurysm

Introduction

Thoracic aortic aneurysms and dissections are highly lethal aortic diseases that can present as emergencies and will require urgent surgical treatment: while the majority of patients with dissection and ruptures will not survive without surgical repair, post-operative mortality may remain as high as 25%, in addition to serious complications such as stroke and spinal cord injury (1). While surgical advancements have improved morbidity and mortality rates over time, non-surgical management and preventative action can further reduce the burden of TAAD on our society. Of the 5160 deaths in the United Kingdom attributed to aortic aneurysms and dissections in 2017, the majority occurred in the elderly: with the rise of senescence, it is important to address the physiological factors that contribute to these aortic diseases early to prevent morbidity and mortality (2).

Both diseases within TAAD often occur concurrently and both owe its aetiology to aortic wall dysfunction (3). The wall dysfunction also predisposes the formation of thoracic aortic aneurysms (TAA), which naturally enlarge and further increase the risk of thoracic aortic dissection (TAD) (3). At the centre of both diseases lies the aortic wall, and like arteries, it is divided into tunica intima, media and adventitia. Thoracic aortic aneurysms affect all three layers of the vessel and is applicable to any dilatation of over 1.5 times its normal size anywhere from the aortic root to the beginning of abdominal aorta (4, 5). TAAs most commonly affect the aortic root and

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ascending aorta (60%) but can also affect other segments such as descending aorta (35%) and aortic arch (<10%) (6). Despite being similar pathologies and sharing some aetiologies, such as connective tissue degeneration and biomechanical changes, TAA distinguishes itself from the signature inflammatory changes in abdominal aortic aneurysms (AAAs) with its heavier genetic involvements (5, 7). Alongside well-known genetic syndromes, there are at least 15 highly penetrant genetic mutations that predisposes TAAD (3, 8). While the eventual outcome is the loss of aortic shape and gradual development into TAAD, dissection can also develop independently of aneurysms (8). TAD occurs when there is intramural haemorrhaging and propagation between the intimal and medial layer of the aorta, allowing blood to pool within a false lumen. Like TAA, TAD can occur anywhere along the aortic arch, ascending and descending aorta and are denoted by DeBakey or Stanford classification systems (8). As expected, aetiology of TAA and TAD overlaps and are broadly classified by mechanisms: wall stress and medial degeneration. Increased wall stress, most commonly due to hypertension, is known to cause both TAA and TAD is prevalent in two-thirds of all patients with TAD. Conditions such as Marfan syndrome, Ehlers–Danlos syndrome, Turner syndrome and aortic inflammation affect aortic wall integrity and cause medial wall degeneration, contributing to the development of TAD (8). Regardless of aetiology, both diseases can present similarly as a severe central chest pain that radiates to the back and calls for immediate treatment (1).

Typically, the first step in managing TAAD in stable patients is to slow the worsening of aneurysm or dissection through controlling their risk factors. This involves optimising the blood pressure and lipid control as well as making lifestyle changes such as smoking cessation and avoidance of strenuous exercises (8). This can also be achieved medically: through the use of β-blockers, angiotensin-II receptor blockers and angiotensin-converting enzyme inhibitors, TAAD can also be managed medically, the effects however were based on relatively small studies (8, 9, 10). Even with optimised management, the thoracic aorta can continue to grow and will experience a sharp increase in risk of rupture, dissection and surgical mortality once it reaches 6 to 7 cm in diameter (8). Unlike other variants, type A aortic dissection is an emergency: almost 48.6% mortality occurring before hospital assessment and intervention only narrowly improves patient survival rate (3, 11). This provides the basis for regular monitoring of TAAD and early prophylactic surgical repair for the best outcome. A myriad of surgical approaches are employed in repairing TAAD; ascending and aortic arch TAAD are typically treated with open repairs, whereas descending TAAD are treated with endovascular stent-grafts.

Like any other disease, prevention is superior to treatment and a better understanding of TAAD will improve upon our control over disease development and progression, delivering better patient outcomes. The underlying aetiology of TAAD development can be broadly classified into several causes: genetic, telomere, biomechanical and inflammatory (Fig. 1). To understand the aetiology governing the mechanisms of TAAD formation, there is active research into probable causes such as genetic association, telomere length, biomechanics and inflammation. This literature review will explore the interaction and evidence behind these factors that contribute to the formation and progression of thoracic aortic aneurysms and dissections.

Genetics of aortic aneurysm and dissection

With TAAD being the result of dysfunctional physiology of the aortic wall, it follows that there are genetic factors involved in altering the wall function and predisposing patients to TAAD. There are several known genetic causes that can cause medial degeneration which in turn precipitate the formation of TAAD, with the most famous being Marfan, Loeys–Dietz and Ehler–Danlos syndrome (12). As many patients with these syndromes develop TAAD, they are noted to have heritable or familial forms of TAAD to signify their background aetiology. While up to 20% of individuals with a family history of TAAD do not have a known syndrome we only know of a handful of associated genes, with many more yet to be uncovered (3, 11, 12).

Genetic syndromes and TAAD

Syndromic causes are the chief associated or causative pathologies behind the genetics of TAAD: all identified syndromes have effects on vessel integrity and the associated TAAD sudden deaths commonly plague these patients. Marfan syndrome (MFS, OMIM 154700) is an autosomal dominant connective tissue disorder that typically affects the skeletal and cardiovascular system (12,13). While MFS is associated with Marfan locus on chromosome 15, presentation remains highly variable (14, 15). Central to its pathophysiology is the defect in fibrillin-1 gene (*FBN1*) which is responsible for up to

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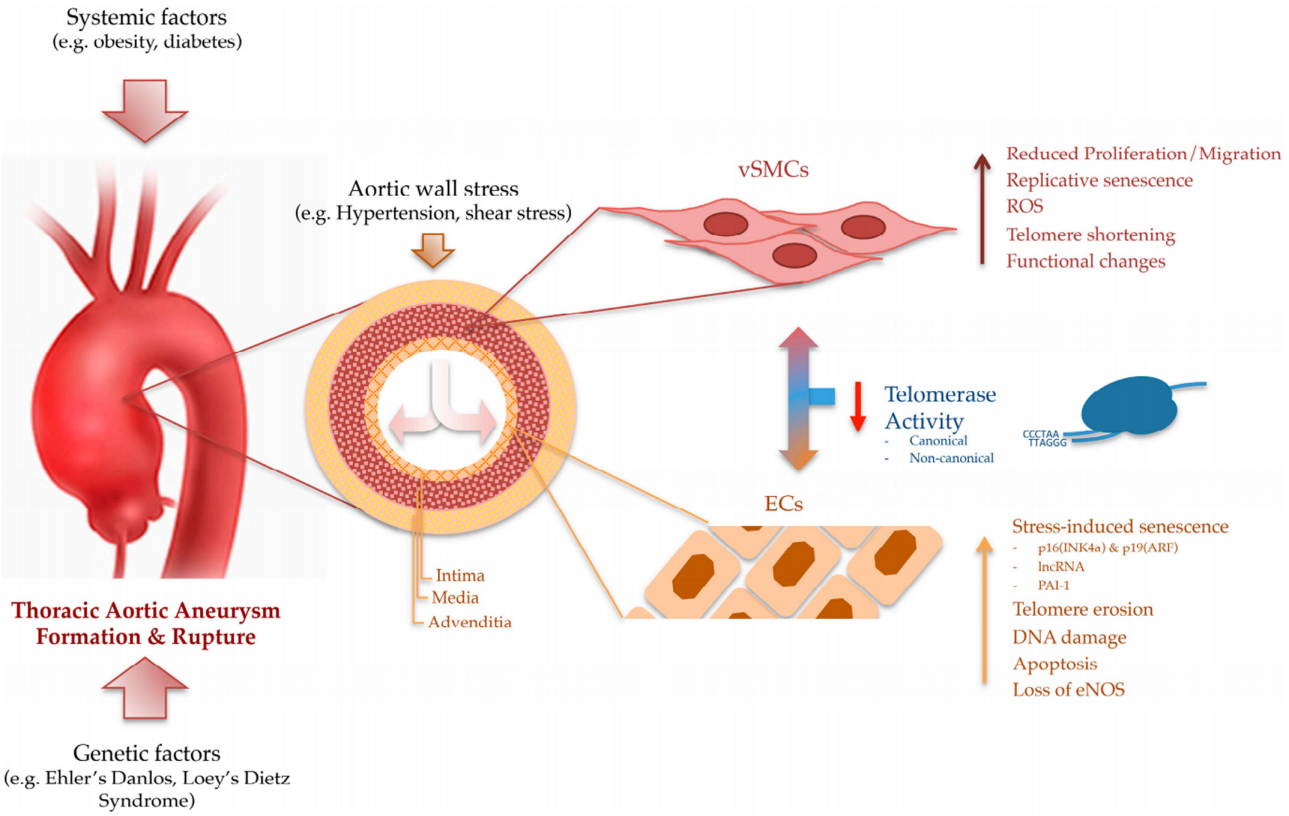

Figure 1
Overview of various contributing factors towards formation of thoracic aneurysm (44).

93% of all MFS cases; *FBN1* at 15q15–q21.1 encodes for fibrillin-1, a glycoprotein within extracellular matrix (ECM) microfibril such as elastic fibres of the medial wall of the aorta and is abnormally metabolised in most MFS patients (14, 15, 16). This indirectly involves TGF-β, a molecule that contributes to TAAD development through regulating MMP activity and extracellular matrix breakdown. FBN1 regulates TGF-β receptors and serves to inhibit TGF-β, hence, defects in FBN1 indirectly raises TGF-β and lead to increased TAAD formation. Despite uncovering pathophysiology of FBN1, approximately 10% of Marfan syndrome cases are caused by genetically unknown origins (17). Similar to FBN1, defects in *FBN2* causes a Marfan-like syndrome called Beals syndrome or congenital contractural arachnodactyly. This gene lies on chromosome 5q23-31 and also introduces a similar instability through affecting ECM microfibrils (18, 19).

Another commonly associated pathology is Ehlers–Danlos syndrome (EDS) characterised by fragility and rupture of arteries, intestines and uterus (20). Vascular EDS (type IV, OMIM# 130050) has the worst prognosis of all EDS types due to vascular complications with type III collagen dysfunction. This is an autosomal dominant pathology that primarily affects the ECM of the cardia and vasculature through defective type III procollagen gene (*COL3A1*), which is responsible for almost all cases (21). Type IV is the only to affect type III procollagen and is associated with a history of sudden deaths in close relatives (21). As the elastic property of vessel walls are dependent on the abundance and function of type III collagen, disruption in procollagen is responsible for their generalised vascular fragility and predisposition of TAAD.

Similarly, patients with Turner syndrome (TS) are predisposed to a myriad of cardiovascular malformations: aortic dissection, coarctation, congenital bicuspid aortic valve, persistent left superior vena cava and various left-sided malformations are common and lead to 41% of cardiovascular events in TS patients (22). Aortic root dilatation is often present and thought to be blood pressure dependent, with it eventually forming aneurysms and dissections (22, 23). Hypertension aside, congenital bicuspid aortic valves, coarctation and short stature of female TS patients also predisposes aortic dilatation and dissection (22, 23, 24). Ascending aorta diameter in short female TS patients are significantly wider than healthy cohorts and is responsible for increased incidence of up

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to 618 cases/100,000 woman-years compared to under 3/100,000 annually (25).

Loeys–Dietz syndrome (LDS) is a relatively new autosomal dominant syndrome that describes the effects associated with mutations in transforming growth factor beta receptor genes 1 and 2 (*TGFBR1/TGFBR2*) (26). LDS presentation can vary, with type 1 being Marfan-like and type 2 similar to EDS. Regardless, loss of TGFβ function and subsequent dysregulated signalling pathways are thought to affect TAAD development through alteration of collagen and elastin metabolism.

Another relatively rare condition, multisystemic smooth muscle dysfunction syndrome, is a defect in *ACTA2* that manifests as decreased contractility of smooth muscle cells (SMC) (27, 28). In one study, a defective *ACTA2* is seen in 14 of 98 unrelated TAAD families, of which most of the individuals died of dissection (29). Its association with TAAD is proposed to be defective α-actin polymerisation which affects actin fibre stability in SMC of thoracic aorta (28). The commonly known syndromic genes and pathophysiology are displayed in Table 1.

Non-syndromic genetic association with TAAD

Many patients do not have a syndromic cause but present with a strong familial history and some are regarded as a type called familial TAAD. While syndromic genes provide a myriad of clinical presentation and signs, individual genes are more difficult to identify. Through genetic screening of families with high TAAD incidence, some genes have been identified to be common among these families, but there are also unique mutations only present in selected families. However, not all the identified genes have been thoroughly investigated to elucidate their exact pathophysiology. The various genetic defects affect the physiology central to TAAD such as impairment of SMC function by *FOXE3* and *MAT2A* or ECM disruption by *MFAP5* (30, 31, 32). The known non-syndromic genes and pathophysiology are displayed in Table 2.

Telomere and its role in genetic disruption

With such prominent role of genetics within the formation of TAAD, it is also important to consider the regulation of genetic materials which governs the underlying cellular processes. Genetic stability is maintained by telomeres which are tandem DNA repeat sequences that stabilises chromosomes (44). While telomeres serve their function, their length is reduced after every replication, essentially giving each chromosome a limited lifespan. This represents the biological senescence of cells and is generally limited to approximately 50 divisions. Telomere shortening in age-related diseases such as cardiovascular diseases have been proven to reflect cellular turnover and shows potential within TAAD cases (44). The biological ageing effect of telomere attrition can also be caused by oxidative stress, damaging repair mechanisms present in certain cells lineages where telomerase restores the tandem repeat sequences.

Preclinical studies have identified age-related endothelial cell (EC) and SMC dysfunction that contributes to the vascular damage seen in AAA (44). Several stress-induced senescence markers and vascular mediators were studied in mice and shown to have a role in regulating telomere length (44, 45, 46). With similar mechanics at play in AAA, telomere shortening in EC, SMC and leukocytes may also be crucial to TAAD development (44). However, there is currently a lack of thoracic aorta specific research and much of our understanding is built upon our knowledge on AAA.

Endothelial cells and smooth muscle cells

The structural integrity of aorta is heavily dependent on the physiology of EC and SMC: with EC exerting influence over development of SMC, they regulate the vascular tone, blood pressure and vasculogenesis (47, 48). A study by Cafueri *et al.* identified that patients with AAA had significantly shorter telomere lengths in the EC and SMC when compared to control groups (49). The effects of telomerase in EC of abdominal aorta has been studied by Dimitroulis *et al.* associating attenuated telomerase expressions with AAA (50). Their findings are in line with a study by Okuda *et al.* who found that higher rates of telomere attrition is associated with accelerated senescence of EC (51). Okuda *et al.* also identified differences in the rate of telomere shortening between various segments of the abdominal aorta and attributed the difference in cell turnover to shear wall stress of the distal segments. Similarly, Wilson *et al.* showed that telomeric DNA is significantly reduced in AAA biopsies compared to normal aortas of cadaveric donors (52). As most of the current literature focuses on AAA specifically, Blunder *et al.* investigated telomeres in TAA: telomeric lengths of SMC in TAA aortic valves demonstrated to both reduce proliferation and migration of aneurysmal SMCs (53). Their demonstration of telomere shortening in TAA compared to controls also corroborates with the available literature on AAA, supporting potentially similar telomere biology at play.

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Table 1 Syndromic genetic associations with thoracic aortic aneurysms and dissections.

Syndrome	Gene loci	Presentation	Pathophysiology
Congenital contractural arachnodactyly (33)	*FBN2*	TAAD	Disruption of ECM microfibril through fibrillin-2
Ehlers-Danlos syndrome (EDS) type IV (20)	*COL3A1*	TAAD	Defective type III procollagen disrupts collagen III deposition and function
Loeys-Dietz syndrome (26)	*TGFBR1*, *TGFBR2*	TAAD	Alters TGF-β signalling dysregulates collagen and elastin physiology
Marfan syndrome (14, 15)	*FBN1*	TAAD	Disruption of ECM microfibril through fibrillin-1
Multisystemic smooth muscle dysfunction syndrome (27, 28)	*ACTA2*	TAAD	Defective α-actin affects aortic SMC function
Turner syndrome (22)	Partial or complete loss of X chromosome	TAAD	Congenital cardiac and vascular malformation changes haemodynamics

Leukocytes

Another significant class of cells affected by dysregulation of telomere are leukocytes: abnormality with inflammatory effector cells may explain TAAD pathogenesis. Multiple studies have identified association between leukocyte telomere length and vascular degeneration, as well as a varied relationship with TAAD. There is contrasting evidence on leukocyte telomere lengths as both lengthening and shortening have been observed in TAA. Huusko *et al.* demonstrated lengthened leukocyte telomere in TAA and was accompanied by a statistically significant rise in telomerase expression as a compensatory mechanism (54). This contrasts with the work by Balistreri *et al.* and Blunder *et al.* who identified shortened telomere lengths in TAA (53, 55). Similarly, Yan *et al.* found that leukocyte telomere in TAD is consistently shorter than controls across various age groups ($P<0.05$) and suggests potential to predict aortic dissections (56). With the conflicting evidence on TAAD, and lack of large studies, more research is required to determine the nature of relationship between leukocyte telomere and TAAD development.

Mechanobiology of aorta

Mechanobiology of the aortic wall is a crucial aspect of TAAD development as it is chiefly mediated by medial degeneration. The tunica media layer is mostly occupied

Table 2 Non-syndromic genetic associations with thoracic aortic aneurysms and dissections.

Gene loci	Association	Presentation	Pathophysiology
FBN1 (16)	Present in 3.9% of non-syndromic TAD	TAAD	Affect ECM microfibrils and causes sporadic TAD in non-Marfan patients
FOXE3 (30)	Autosomal dominant inheritance	TAAD	Reduced SMC density through impairing development and increasing apoptosis
LOX (34, 35)	Genetic predisposition in 25% of familial TAAD	TAAD	Deficiency of LOX or inhibition of lysyl oxidases
MAT2A (31)	Strong familial association	TAAD	Defective MAT IIA enzyme impairs methylation reactions in SMC
MFAP5 (32)	Strong familial association	TAAD	Mutation dysregulates TGFB/BMP signalling pathway
MYH11 (36)	Strong familial association	TAAD	Upregulation of IGF-1 and angiotensin II without increased TGFB
MYLK (37)	Strong familial association	TAD	Disruption of calmodulin and kinase activity of SMC
PRKG1 (38, 39)	Strong familial association	TAD	Increased PKG1 decreases contractility of aorta SMC
SMAD3 (40)	Responsible for 2% of TAAD	TAAD	*SMAD3* haploinsufficiency disrupts differentiation and collagenous function of myofibroblasts
AAT1/FAA1 (41)	Genetic predisposition	TAAD	Identified association with loci at chromosome 11q23.2-q24
AAT2/TAAD1 (42)	Genetic predisposition	TAAD	Identified association with loci at chromosome 5q13-14
Unidentified gene (43)	Genetic predisposition	TAAD	Marfan-like condition associated with loci at chromosome 3p24-25

SMC, smooth muscle cell; TAA, thoracic aortic aneurysm; TAD, thoracic aortic dissection; PKG-1, type I cGMP-dependent protein kinase.

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by the ECM, containing layers of structural proteins such as elastic lamellae and collagen fibre, as well as fibronectin and laminin, SMCs and glycosaminoglycans (7, 57, 58). TAAD is histologically characterised by the degeneration of elastic fibres, remodelling of collagen matrix, loss of SMC and pooling of glycosaminoglycans (59). As each of these are an integral component of the aortic wall, their dysfunction can lead to markedly reduced distensibility and long-term stability, leading to aneurysms and dissections (60).

To maintain vascular function, the aortic wall must be able to accommodate rhythmic pressure rises exerted by ventricular contractions. The luminal pressure is translated into circumferential and axial stress, at approximately 150 kPa, and is drastically increased in aneurysms which surpasses 450 kPa (60). Normally, under a high pressure, the aortic wall deforms isochorically and stretches, with stiffness directly proportional to the strain on the aorta. When aneurysms occur, the wall stiffness no longer varies and results in an increased distensibility and aortic compliance whereby the loss of stretching or wall stiffness at high pressure loci increases likelihood of aneurysm and dissection formation (60).

Elastin, collagen and smooth muscle cells

Elastic fibres of tunica media is made of several structural proteins such as elastin and fibrillin, both of which are central to elastogenesis and longer term stability of the fibre itself (61). As their deposition occurs perinatally, damage to elastin leaves a lasting impact due to the lack of further repair mechanisms after puberty (62, 63). Degradation and fragmentation of these elastic fibres reduces aortic resilience, compliance and distensibility and can be caused by a combination of mechanical wear and tear over a lifetime and inflammatory degradation via MMP upregulation (63, 64). Apart from elastic fibres, collagen is also involved in aortic wall pathologies. The collagen present is type I and III, which are responsible for strength and stiffness by acting as a protective sheath to bear majority of circumferential and axial stress during high pressure in addition to shielding the vascular SMC from excessive stress (65). Loss of these collagen would also lead to instability and predisposes the aorta to rupture (60). Unlike elastin, collagen has a much shorter half-life as active degradation and deposition allows structural adaptation to occur, making it less prone to mechanical wear and tear (66). However, it can still be affected by defective genes, expression and arrangement which compromises aortic wall strength and lead to stiffness (67). Pathologies that affect elastic fibre and collagen predisposes a person to TAAD, as demonstrated by the aortic fragility in EDS where collagen type III is affected (12, 60). Increasingly disorganised collagen and fragmented elastic fibre is seen in both physiological ageing and in TAAD, leading to the loss of stiffness variation along the aorta. The resultant aorta is then unable to modulate and cope with the blood pressure and wall stress, leading to aneurysm and dissection risks (67).

The development of TAAD can be attributed to compromised wall integrity, a combined consequence of compromised aortic wall integrity and impaired repair mechanisms. Central to these processes are SMCs and adventitial fibroblasts which deposit and organise the ECM to maintain a physiological pressure and respond to haemodynamics changes (60). Each type of cell utilises different integrins, a class of transmembrane proteins responsible for bind to constituent parts of the ECM (68). Deficiency in integrins reduces the ability for cells-to-bind effectively to the ECM which leads to an overall reduction in contractile force (68).

Glycosaminoglycans

While loss of elastin, SMC dysfunction and collagen remodelling is common to all aneurysms, only TAD leads to glycosaminoglycans (GAG) pooling (69). The structural changes in TAAD are not limited to elastic and collagen fibres but also uniquely includes the accumulation of glycosaminoglycans which increases the risk of delamination and ruptures. GAGs are negatively charged repeating disaccharide units that are often overlooked as a contributor to TAAD due to their association with compression rather than tension (59, 69, 70). Compressive stress in the aorta is comprised solely of radial stress at approximately 10 kPa and peaks at 60 kPa when pressure distribution is asymmetrical along the aorta, providing a stark contrast to axial and circumferential stresses of 150 kPa (60, 69).

GAGs often accumulate in regions where elastic fibres and SMCs have degenerated, leading to a phenomenon called GAG pooling. This produces excessive pressure via the Donnan effect, where the equilibrium is affected by an electrostatic gradient established by the negatively charged GAGs (69, 70). The ionic gradient changes regional distribution of interstitial water, producing a swelling pressure of magnitude possibly exceeding axial and circumferential stress and is dependent on the charge density within the region (59). This leads to three distinct phenomena: separation of elastic lamina,

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loss of wall tensile capacity and non-uniform stress distribution along the aorta. The swelling pressure caused by ion gradient contributes to the separation of elastic lamellae from media, as demonstrated by Lesauskaite *et al.* where an increased separation distance of elastic lamellae is observed at areas of pooled GAGs (58, 59). This renders the aortic wall vulnerable to subsequent dissection and rupturing. Donnan swelling also affects SMC interactions with elastic fibres of the media1, impacting SMC mechanotransduction and thus affecting various signalling pathways of ECM metabolism, resulting in deleterious effect of hemostasis and homeostasis (69, 70). Loss of tensile capacity occurs as GAGs displace elastic fibres, collagen and SMC, interrupting regular function. This essentially replaces tensile carrying molecules and increases compressive capabilities at the cost of tensile capacity, manifesting as reduced maximum axial and circumferential load before dissection occurs (58). Finally, GAG pooling at specific regions result in the geometric discontinuity and irregularity along the aorta, giving rise to focal stress concentration where local pressures can increase by several fold (58, 69, 70). In some instances, as seen in MFS, additional aortic wall stiffening, elastic fibre fragmentation and collagen remodelling can exacerbate the effects of irregular stress distribution (65).

Inflammation of the aortic wall

In addition to genetics, inflammatory component of TAAD should also be considered to better understand the role of immunological effector cells in medial degeneration. Pro-inflammatory cells are central to the pathophysiology and express cytokines that directly trigger aortic wall degradation through events such as SMC apoptosis and ECM proteolysis.

Mechanics of inflammation

The underlying trigger of inflammatory aetiology of TAAD is still debated. Some hypothesise that the presence of excess lipids in the aorta increases the number of inflammatory cells: the inflammatory response to lipids, or a product of lipid oxidation, results in degradation of the media and hence increases the risk of TAAD (71, 72). Others have found that autoimmune reactions produce aortic aneurysms based on the established correlation between inflammatory aortic aneurysms and autoimmune diseases (73). While the trigger is yet to be uncovered, active research continues to unravel the mechanisms involved.

Under physiological stress observed in TAAD, apoptotic and inflammatory signalling pathways are activated in aortic cells. Moreover, the pro-inflammatory state, and presence of apoptotic SMCs, drives inflammatory cells such as lymphocytes and macrophages to infiltrate the tunica media via the adventitia (74). This results in the destruction of wall structures as well as progressive enlargement of aorta which predisposes rupture and dissection. Apoptotic SMCs play a role in recruitment of such cells, as well as secretion of pro-inflammatory proteases, such as elastase and collagenase, that facilitate degradation of ECM (74, 75).

Cytokines

Inflammatory cells that infiltrate the aortic media secrete various inflammatory mediators such as interleukins (IL) and tissue necrosis factor alpha (TNFA) (72, 76, 77). Together with these effector cells, the mediators upregulate matrix metalloproteinase (MMP) expression, including MMP1, MMP2 and MMP9, which are known to degrade elastin. Additionally, MMP3 has been observed to have a collagenolytic role in TAAD and AAA (78, 79, 80). This results in medial degeneration and subsequently leads to dissection (74, 81). IL3 secreted by T lymphocytes, mast cells, CD19+ B lymphocytes and SMCs stimulates the production and secretion of MMP12 also known to degrade ECM (81). TNFA and interferon gamma (IFNG) are secreted by infiltrating lymphocytes which stimulate macrophage pro-inflammatory functions and upregulate MMP secretion, causing ECM remodelling (72, 79, 82). Other released pro-inflammatory molecules include reactive oxygen species that impairs endothelial functions and progresses development of cardiovascular disorders by breaking down structural components of tunica media (80, 83).

Transforming growth factor beta

A key cytokine involved in mediating aortic stability is transforming growth factor beta (TGFB), a family of molecules with seemingly conflicting effects on TAAD development. TGFB is a superfamily of ligands known to affect matrix degradation and vascular remodelling, causing the myriad of cardiovascular malfunctions in diseases such as MFS and LDS (77, 84, 85).

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Its effects manifest via activation of various signalling pathways, both SMAD dependent and independent. As a whole, TGFB regulates the function of SMCs and endothelial cells, including proliferation, migration and matrix metabolism (85, 86).

Sources demonstrate TGFB as a significant molecule involved in the hallmark features of TAAD, particularly in those with MFS and LDS (84, 87). For example, TGFB1 is thought to promote TAAD development and is found elevated in human and animals with aortic aneurysm (88). This results in the degeneration of ECM through MMPs and stimulation of collagen production, both of which are traits exhibited in TAD patients (75). TGFB releases MMP2 and 9, resulting in further elastin degeneration, while MMP3 degrades collagen resulting in similar consequences (79, 80, 89). TGFB is also observed to decrease contractile protein expression in thoracic aorta SMC and fibrillin assembly of the ECM, reducing aortic distensibility and elastic fibre numbers.

However, observations of increased TGFB signalling in aortic aneurysm tissue lacks direct evidence supporting TGFB activity as the underlying mechanism of TAAD and causality is yet to be established (84, 90). The elevation of TGFB may be considered a homeostatic response to limit aorta damage: SMC expression of TGFB in murine aortic tissue displays protective effects by limiting aortic aneurysm expansion in early MFS development (91, 92). More recent clinical research has shown TGFB signalling to be protective against thoracic aorta dilatation and aneurysms. A study by Theruvath *et al.* associated the expression of TGFB with a downregulation of MMPs and upregulation of MMP inhibitors such as TIMPs, resulting in decreased medial degeneration (93). Hence, while TGFB signalling suppresses pro-inflammatory activity and reduces degenerative processes, its overexpression causes an accumulation of SMC, collagen and elastin which resembles the histological characteristics seen in TAAD (90).

In addition to aneurysms, there are also studies that recognise mutations of TGFB as the cause of associated syndromes such as MFS and LDS. Mutation within the TGFB signalling network of proteins such as FBN1 results in LDS and MFS, while mutations in TGFB receptor structure also lead to TAAD (77, 87, 94). For instance, mutations in TGFB3 genes causes a loss of TGFB3 function and is a feature heavily associated with TAAD and mitral valve diseases (94). Moreover, a systemic blockade of TGFB signalling pathway is shown to significantly increase aneurysm risk and severity while neutralisation of TGFB via angiotensin II results in fatal aortic dissection (90, 95). Regardless of its effect, TGFB is an essential component of stable vascular development. With different studies expressing contrasting opinions on the role of TGFB, further research is required to determine its exact role in TAAD formation. The most recent literature on TGFB and findings are displayed in Table 3.

Overall, a pro-inflammatory environment accompanied by death of SMCs reduces ECM homeostasis and decreases maintenance of the aortic wall (96). As vascular SMC ages and calcifies, it bears the mark of senescence whereby mitosis plateaus and pro-inflammatory cytokines are increased drastically (97). The senescence of SMC is another feature typically in aneurysmal vasculature: Once induced by stress signals and reactive oxygen species, secretion of pro-inflammatory cytokines follow and leads to medial degradation (98, 99). It is further observed that senescent cells may influence non-senescent cells to exhibit similar pro-inflammatory behaviour as well (100). This all results in aortic inflammation and weakens the wall (8, 75). Additionally, the degradation of the aortic media induces strong leukocyte chemotactic signals, promoting local inflammatory cell infiltration and further

Table 3 Overview of the most recent literature on TGF-β and its association with TAAD.

Author, year	Population (*n*)	Subject	Findings
Wang *et al.*, 2017 (77)	602	Human	Reduction in *SMAD4* impairs TGF-β signalling pathway is involved in progression of TAAD
Scola *et al.*, 2014 (89)	144	Human	TGFB2 single polymorphism is associated with TAAD in women
Bertoli-Avella *et al.*, 2015 (94)	43	Human	TGFB3 ligand causes syndromic aortic aneurysms
Yang *et al.*, 2016 (84)	51	Murine	Decreased TGFB receptor expression on SMC disrupt aortic wall homeostasis and cause TAAD
Angelov *et al.*, 2017 (90)	75	Murine	Loss of TGFB receptor expression on SMC accelerated various thoracic aorta pathologies
Hu *et al.*, 2015 (101)	28	Murine	Loss of TGFB receptor expression on SMC accelerated TAAD
Chen *et al.*, 2016 (95)	119	Murine	TGFB inhibition in presence of angiotensin II facilitates development and rupture of TAA

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release of pro-inflammatory cytokines, such as IL6 and TNFA, compounding the damage inflicted on the aorta.

Summary and future direction

The importance of TAAD has become increasingly relevant in recent years and further research into this subject is crucial to reduce morbidity and mortality. A myriad of factors are involved in the development and progression of TAAD, all of which will require further exploration to understand the interaction between factors. Genetic basis of TAAD can be traced back to a variety of genetic syndromes despite being occasionally associated with other genes. Alternatively, an inflammatory aetiology can play a role and is also affected by genes and telomere activity. Furthermore, fluid dynamics and biomechanical properties add complexity to their interactions. The resultant outcome typically revolves around the disruption of collagen and elastin metabolism as well as changes to endothelial cell and smooth muscle cell physiology. Despite increasing attention in this area, our current knowledge remains limited, with knowledge of aneurysms often extrapolated from literature on AAA and murine studies, which may not necessarily be applicable to TAAD.

Future research should aspire to conduct larger scale studies to examine thoracic aortic pathologies specifically and is feasible through increasing genetic screening of apparently unaffected and undiagnosed relatives of those who suffer TAAD. This would not only facilitate correlation between genes and TAAD incidence, but also its relationship with severity. With developments in gene therapy becoming increasingly feasible, the challenge now lies in identifying all the associated gene and individual pathogenesis mechanism which may eventually become therapeutic targets to address.

Conclusion

This review has explored the current research regarding different aspects of TAAD, all of which will require further exploration: the lack of studies specific to thoracic aorta hinders our knowledge on TAAD and must receive greater emphasis to improve our understanding. The process of genetic screening continue to gain popularity as awareness of TAAD increase, helping to both facilitate patient management as well as provide larger patient groups to further identify genes responsible for TAAD. With much of the aetiologies, such as TGFB and effects of telomere length, still debated, it is crucial to conduct larger studies and reach a consensus. All-in-all, the ongoing debate on TAAD will continue to drive innovative research and improve our understanding.

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