Thoracic Aortic Aneurysms

Subjects: Others

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Thoracic aortic aneurysms (TAA) are permanent and localized dilations of the aorta that predispose patients to a life-threatening risk of aortic dissection or rupture. The identification of pathogenic variants that cause hereditary forms of TAA has delineated fundamental molecular processes required to maintain aortic homeostasis. Vascular smooth muscle cells (VSMCs) elaborate and remodel the extracellular matrix (ECM) in response to mechanical and biochemical cues from their environment. Causal variants for hereditary forms of aneurysm compromise the function of gene products involved in the transmission or interpretation of these signals, initiating processes that eventually lead to degeneration and mechanical failure of the vessel. These include mutations that interfere with transduction of stimuli from the matrix to the actin–myosin cytoskeleton through integrins, and those that impair signaling pathways activated by transforming growth factor-β (TGF-β).

Keywords: aortopathy ; aneurysm

1. Introduction

Aneurysms are permanent, localized dilatations of an artery greater than 50% of the normal diameter. They progressively dilate while remaining mostly asymptomatic until a life-threatening rupture and/or dissection occurs [1]. Prophylactic surgical repair remains the only proven method to prevent risk of death caused by mechanical failure of the vessel [2]. Aneurysms can develop both in the thoracic and abdominal aorta [3]. Aneurysms that affect the abdominal aorta are more common, tend to occur in older individuals, and have no known monogenic cause, although multiple candidate risk loci have been reported [4][5][6]. While less common, thoracic aortic aneurysms (TAA) can develop in the absence of cardiovascular risk factors, affect younger individuals, and have a higher degree of heritability [6][7]. Although a hereditary predisposition to TAA confers an increased risk of aortopathy to all segments of the vessel, pathogenic mechanisms can differ depending on the specific aortic location [8][9]. For example, dissections of the thoracic descending aorta can occur even when dilation is limited or absent and as a complication of proximal aortic repair [10][11][12]. Hereditary forms of TAA are subdivided into syndromic and non-syndromic depending on the presence or absence of manifestations in other organ systems [13]. Syndromic forms of TAA occur in patients affected by connective tissue disorders such as Marfan syndrome (MFS) and Loeys–Dietz syndrome (LDS) [13], all of which have manifestations in organ systems other than the aorta. In contrast, TAAs in hereditary non-syndromic thoracic aortic disease are not usually associated with overt defects in other connective tissues [13]. Several causative genes for both syndromic and non-syndromic TAA have been identified, leading to a better understanding of the mechanisms by which this condition develops [14].

2. Adaptive and Maladaptive Responses in TAA: Implications for Therapy

We have a limited understanding of the compensatory mechanisms activated in response to germline TAA-associated mutations. Feedback responses attempting to offset the negative consequences of a given genetic variant are active throughout prenatal and postnatal development and might significantly modify the structural, cellular, and molecular properties of the adult aorta. Mechanisms that are adaptive early, such as the activation of secondary pathways that compensate for the initial deficiency, might become maladaptive later on due to divergent effects on adult versus embryonic tissues, over-activation, or secondary activation of deleterious pathways. This might be especially true for mutations that impair signaling involved in morphogenesis, such as TGF-β and Notch signaling, given that the mitigation of defective signaling in these pathways is a condition necessary for the development of vascular structures and survival [15][16][17]. Additionally, while it is tempting to assume that all the phenotypic changes observed in TAA at the structural, cellular, and molecular level are contributing factors to disease, some may represent ongoing beneficial compensatory responses.

2.1. Adaptive and Maladaptive Roles of “Aortic Stiffness”

Loss of elastin and the increased deposition and crosslinking of collagen during aneurysm development translate into biomechanical changes that include reduced distensibility and increased stiffness of the aorta [18]. Changes in stiffness modulate VSMCs phenotypes through integrins and focal adhesions; although stiffness is generally associated with the retention of a “contractile” phenotype, excess stiffness can also increase sensitivity to growth factors, such as PDGF, which promotes a “synthetic” phenotype, and enhanced ECM stiffness has been shown to promote a switch from a “contractile” to a “synthetic” phenotype through the downregulation of DNA methyltransferase 1 [19][20][21][22].

Perhaps unintuitively, increased stiffness (resistance to deformation) can associate with decreased vessel strength (ability to withstand stress without breaking), with one study measuring an approximately 30% decrease in vessel strength accompanied by a 72% increase in stiffness in aneurysmal versus nonaneurysmal ascending aorta [23][24]. Correlations between increased stiffness and aortic dilatation have been reported in numerous studies of both patients and mouse models of TAA [25][26][27][28][29][30][31][32][33][34][35][36][37][38][39].

Although measures of distensibility and circumferential strain lose predictive power once aortic diameter is included in the analysis, a recent study of one hundred and seventeen MFS patients showed that measurements of longitudinal strain in the proximal aorta was a predictor of adverse aortic events (such as elective aortic root surgery or dissection), thus providing support to the notion that aortic stiffness could be considered for the stratification of patients based on risk [25][40][41].

These observations may suggest that increased collagen deposition and crosslinking is uniformly deleterious in TAA. However, other studies have shown that collagen deposition, especially in the adventitial layer, can be protective and part of beneficial “scar repair” mechanisms preventing transmural ruptures [18][24][42][43]. Consistent with these latter observations, genetic or pharmacological inactivation of lysyl oxidases, enzymes necessary for collagen and elastin cross-linking, cause or exacerbate aneurysm in patients and animal models [44][45][46][47][48][49][50][51][52]. The detrimental effects of fluoroquinolones on TAA pathogenesis have also been attributed to excess ECM degradation and reduced levels of collagen [53][54][55][56].

Taken together, these data suggest that the deposition of properly crosslinked collagen confers strength to the vessel, thus protecting it from mechanical failure. However, its effect might be highly dependent on the type and quality of collagen and the effect of ECM stiffness on VSMC phenotypes [18][57][58][59][60]. In vitro experiments in which levels of stiffness can be experimentally modulated show that both overly soft and overly stiff substrates fail to support functional focal adhesions and actin–myosin dynamics, and that nanoscale level patterning of substrata that mimics physiological conditions can modulate the effect of stiffness; VSMCs grown on nanopatterned soft substrata had a higher expression of VSMC markers associated with a quiescent, contractile phenotype (smoothelin, calponin-1), and lower expression of inflammatory markers (monocyte chemoattractant protein-1) relative to nanopatterned “stiff” substrata, suggesting that matrix architecture and mechanics have combinatorial effects on VSMC mechanosensing and differentiation pathways [57][58][60].

2.2. Adaptive and Maladaptive Roles of TGF-β Signaling

Work performed in animal models clearly shows that TGF-β signaling is essential for aortic development and morphogenesis [61][62]. Additionally, the ablation of TGF-β signaling in VSMCs by the genetic inactivation of Tgfbr2 postnatally results in aortopathy and dissections as well as an exacerbation of pathology in mice with a pre-existing genetic predisposition to aortic aneurysm, suggesting that postnatal aortic VSMCs require a basal level of TGF-β signaling for homeostasis [63][64][65]. Moreover, as discussed, heterozygous, inactivating mutations in positive effectors of this pathway cause hereditary forms of TAA [66][67][68][69][70][71][72][73][74][75][76]. In consequence of these observations, the increased levels of TGF-β ligand and nuclear pSmad2/3 observed in aneurysmal tissue obtained from patients and models carrying these mutations has been proposed to be part of a “repair” response [5][77].

Beneficial roles of TGF-β in TAA may include the suppression of AT_1R signaling, induction of protective factors such as nexin-1 and proteases inhibitors, and promotion of contractile proteins expression [63][78][79][80][81][82]. In addition, TGF-β-dependent induction of collagen, lysyl oxidases, and other pro-fibrotic factors might contribute to thickening of the adventitial layer, which, as discussed, can be protective [18][48][83][84][85][86][87]. On the other hand, maladaptive effects of excess TGF-β signaling include an induction of glycosaminoglycans and proteoglycan accumulation within the arterial wall, upregulation of proteolytic enzymes that exacerbate ECM destruction, and stimulation of ROS production thorough several mechanisms, including by upregulation of NADPH oxidases (Nox) [88][89][90][91][92][93][94][95][96][97][98][99].

Accordingly, in contrast to the complete inactivation of TGF-β signaling in VSMCs, which unvaryingly enhances pathogenesis, the effect of partial TGF-β antagonism with neutralizing antibodies or by the inactivation of Smad proteins in selected cellular subsets is varied. Systemic TGF-β neutralization had no effect on angiotensin II-induced TAA [100], and it either had a beneficial or dimorphic effect in mouse models of MFS, with perinatal and postnatal antagonism being detrimental and beneficial, respectively [101][102][103]. In a recent study in a MFS mouse model, the beneficial effect of TGF-β neutralizing antibodies was correlated with a reduced expression of Nox4, restoration of normal levels of dihydrofolate reductase, and reduced levels of ROS production [103]. Additional studies in mouse models of hereditary TAA have shown that while germline Smad4 haploinsufficiency is deleterious in MFS, Smad2 deletion in CNC-derived VSMCs is beneficial in a mouse model of LDS [104][105]. Taken together, these data indicate that TGF-β signaling can serve both protective and pathogenic roles in TAA depending both on cell type and stage of disease [106][107].

2.3. Adaptive and Maladaptive Roles of Angiotensin II Signaling

In contrast with direct TGF-β antagonism, treatment with antagonists of AT_1R signaling, such as the angiotensin receptor blocker (ARB) losartan, invariably prevents the development of aneurysm in animal models; this beneficial effect associates with reduced levels of TGF-β ligand, pSmad2/3, and the expression of TGF-β target genes [108][109][101][110][111][112][113]. In addition, the deletion of Agtr1a (gene encoding AT_1R in mice) prevents aortic root dilation in two different MFS mouse models [114][115]. The beneficial effects of AT_1R antagonism in mouse models of TAA have been attributed to its anti-hypertensive effects and to the inhibition of fibrotic, hypertrophic, and mitogenic responses activated by TGF-β and mitogen-activated protein kinase (MAPK) signaling [159,258][105][116]. Additionally, losartan treatment could reduce the AT_1R-dependent secretion of glycosaminoglycans, whose accumulation has deleterious effects on the aortic wall [88][117]. Based on this evidence, several clinical trials have been initiated to test the efficacy of AT_1R antagonism in the treatment of aneurysm in MFS patients. Although the degree of efficacy varied, none of the studies could replicate the remarkable beneficial effects routinely achieved in pre-clinical models; in one trial, the rate of adverse events was higher in the losartan-treatment group than in those receiving a hemodynamically equivalent dose of anti-hypertensive medication [118][119][120][121][122][123][124][125][126][127].

These results raised the possibility that AT_1R signaling might have protective effects in TAA, both directly and through the enhancement of any protective effects of TGF-β signaling [128][129]. For example, the inhibition of AT_1R-dependent collagen deposition and maturation, directly or through TGF-β-dependent pathways, could recapitulate, in part the detrimental effect of lysyl oxidase inhibition with β-amino-propionitrile (BAPN), which causes dissection or rupture in a number of animal models [47][50][51][52][84][85][87][130][131]. Additionally, AT_1R-dependent signaling could be beneficial through stimulation of VSMC contraction [128][132]. Although the potential for beneficial effects of AT_1R signaling need to be considered, other reasons may account for different outcomes in clinical trials relative to mouse models [108][133].

In mouse trials, losartan has been tested primarily in prevention rather than treatment of aneurysm, given that in most studies, the drug is initiated early, before overt disease is apparent; this is not the case for clinical trials, given that many patients have established aneurysms when treatment is started [134]. Additionally, in mouse trials, this drug is administered continuously throughout the day in drinking water or by an osmotic pump, at doses of approximately 50-100 mg/Kg/day; this is relevant because losartan has a short half-life of approximately 2 h [134] and the human equivalent dose [135] for the one used in mice would be 4–8 mg/Kg/day, which is much higher than the 0.4 to 1.5 mg/Kg/day used in clinical trials. In view of these considerations, it is notable that a recent double-blind, placebo-controlled, randomized clinical trial testing the effect of higher doses of irbesartan, an ARB with a longer half-life than losartan, significantly reduced aortic root dilatation in MFS patients [136].

The relative low frequency of adverse aortic events (dissection, rupture, death) makes it difficult to perform clinical trials with sufficient power to assess the effect of treatment on these clinically relevant outcomes, and most trials rely on the measurement of aortic size or growth to assess efficacy. Despite the statistical limitations, the most recent metanalysis of available data showed that AT_1R antagonism slows the progression of aortic root dilation and is not associated with a statistically significant difference in adverse aortic events [32][137]. Additionally, a recently published long-term follow-up of the multicenter COMPARE trial, which originally reported a small but significant reduction in aortic root dilatation [138], showed that losartan treatment in MFS patients was associated with a decreased number of adverse aortic events in the treatment group [138]. Although more studies with sufficient power to confirm this study are both needed and planned, losartan is currently considered an acceptable treatment in combination with β-adrenergic receptor blockers, or when the latter are not tolerated [108][50].

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