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Aneurysm Development in Patients With Bicuspid Aortic Valve (BAV): Possible Connection to Repair Deficiency?

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Review

Thoracic aortic aneurysm (TAA) is manifested by progressive enlargement of the thoracic aorta due to destructive changes in the connective tissue of the media and adventitia in the aortic wall. This process, which is also known as cystic medial degeneration, may ultimately lead to aortic dissection or rupture [1,2]. TAAs are characterized by extensive loss of smooth muscle cells (SMCs) and disruption of elastin and collagen but, unlike abdominal aortic aneurysms, are not associated with intimal atherosclerosis and chronic inflammation [3,4]. Since therapeutic agents that may halt or reverse the process of aortic wall deterioration are absent, the only available therapeutic recommendation is elective surgical intervention.

TAA may occur in the presence of a tricuspid or a bicuspid aortic valve (TAV and BAV), respectively. The pathogenesis of TAA is complex, involving multiple interacting processes, and in this review, we will focus on the latest findings in our laboratory and others, which implies that in spite of phenotypic similarities of the end point of aneurysm, the process of cystic medial degeneration may indeed occur by fundamentally different mechanisms in BAV and TAV patients. Ascending aortic dilatation occurs more frequently and at a younger age in patients with BAV than TAV. It has been estimated that 50%–70% of individuals with BAV develop aortic dilatation. Furthermore, a higher proportion of BAV patients develop other cardiac complications such as aortic valve stenosis and aortic regurgitation [5,6].

Two Hypotheses for BAV-Associated Aortopathy

Two major theories have been postulated to describe the increased prevalence of ascending aortic dilatation, rupture, and dissection in patients with BAV. The first is that a genetic or developmental abnormality present in patients with BAV decreases aortic wall strength and predisposes it to complications. The inheritance of BAV is consistent with an autosomal dominant pattern with reduced penetrance [7,8]. However, BAV is a sporadic disease with a complex pattern of inheritance and the monogenic inheritance has seldom been reported for BAV. Interestingly, Sans-Coma et al. showed that in an isogenic, inbred population of Syrian hamsters, all morphological spectra of aortic valves, from normal tricuspid valves to pure bicuspid valves, could develop in the offspring [9]. This finding implies that BAV formation in Syrian hamsters is a polygenic trait affected by modifiers and that other factors than pure inheritance

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may have a role in the development of a BAV. In humans, a number of genes have been associated to BAV inheritance. Mutations in several genes have been reported to give rise to BAV morphology. These genes are associated with function or integrity of the vessels such as the component of smooth muscle ACTA2 [10] and TGFβ pathway, SMAD6 [11], TGFβR2 [12]. Association between mutation in the NOTCH1 gene and BAV with calcified valves are the strongest genetic links found so far in certain families [7,13–17]. In animal models, the gene coding for endothelial specific nitric oxide synthase NOS3 has been associated with BAV [18]. In humans, although reduction in eNOS expression has been described in BAV patients, mutation in this gene has not yet been identified [19].

The second theory of increased susceptibility for aneurysm formation in patients with BAV is that the higher velocity and eccentric flow jets caused by a BAV can lead to increased shear stress on the ascending aortic wall, thereby increasing the risk of ascending aortic dilatation, dissection, and rupture. The genetic theory has for a long time been the predominant one, however, more recently, with the development of more advanced measurement techniques, the contribution of hemodynamic factors to BAV is also gaining further ground [20–23].

There is still considerable debate in the scientific community as to whether the BAV complications are caused by genetic background or hemodynamics. However, one should bear in mind that this is not a mere theoretical issue and is of major clinical relevance as the outcome may influence the choice of techniques and the time of recommended elective surgery for patients with BAV.

Change of Hemodynamic Signals can Alter the Biological Response in Endothelial Cells and in the Vessels of Animal Models

The focus on hemodynamic forces as a factor regulating blood vessel structure and influencing the development of vascular pathology has a long history, and the notion of association between "disturbed blood flow" and distribution of atherosclerotic plaques was proposed more than four decades ago [24]. We are just beginning to understand how the signals generated by fluid shear stress in endothelium could be transported to the media layer via induction of microRNAs encapsulated in the exosomes [25].

Endothelial cells (ECs) lining the blood vessels are in the forefront of sensing shear stress, and depending on the type of shear stress (chronically elevated, low average, pulsatile, oscillatory, etc.) and flow characteristic the cells are exposed to, a distinct type of gene expression profile is elicited [26–30]. Moreover, ECs can discriminate and respond to spatial shear stress gradients [31] and the response of ECs to magnitude of shear stress is separate and independent of the gradient response [32]. In addition, different types of EC show different patterns of gene expression in response to fluid flow [33,34]. Naturally, the in vitro exposure of ECs to different flow regimes does not fully reflect the in vivo condition [35] and it is not clear what type of flow is relevant for endothelial cells in the intima layer of the aorta of BAV patients.

Although not directly relevant for BAV, surgically manipulated animals have also been used to study the effect of hemodynamic changes on the vessel walls. For instance, aortic banding is a surgical method, in which a flexible polyethylene tube is placed around the aortic root to induce aneurysm in ascending aortas of experimental animals [36]. Hemodynamic perturbations induced by bilateral common carotid artery ligation [37–39] or arteriovenous shunt [40] have also been used and the outcome of these experiments supports that a change in vascular hemodynamics is accompanied by the enlargement and structural disorganization of the vessel walls.

In humans, adaptive remodeling of arteries takes place by a mechanism known as arteriogenesis. Arteriogenesis is the development of collateral circulation and is a natural compensatory mechanism to restore impaired blood flow following stenosis or arterial occlusion. The process is driven by biomechanical changes in blood flow and results in enlargement or remodeling of preexisting vessels running in parallel to the occluded vessels. Angiogenesis and arteriogenesis are driven by distinct, but partially overlapping, cellular and molecular pathways. Like angiogenesis, the induction of inflammatory events is required for arteriogenesis [41].

Clearly, hemodynamic forces driving aneurysms development following aortic banding, carotid ligation, arteriovenous shunts, and vascular remodeling during arteriogenesis in humans are all different from the hemodynamic forces created by the BAV. However, these data collectively hint that the vessels respond to changes in biomechanical forces they are

subjected to; they enlarge when they are chronically exposed to abnormal flow and this is accompanied by structural reorganization.

Molecular and Cellular Differences in the Development of Aneurysm in Patients with BAV and TAV

Morphologically, the dilated aortic wall of patients with BAV is thinner than in patients with TAV [42]. Furthermore, the aortic wall of BAV patients is stiffer and shows impaired aortic elasticity compared with age-matched TAV individuals [43]. In a study performed on pediatric patients with BAV, it was concluded that the elasticity index levels in the patients up to the age of 10 years did not differ significantly from those of the TAV subjects but deteriorated progressively with age [44].

The concept of "asymmetrical aneurysm" was first introduced by pioneering work of Della Corte's laboratory, which showed that the medial degeneration in the aorta of BAV patients occurred earlier and in the absence of substantial dilation. In addition, the dilatation was more severe in convexity than in the concavity when BAV patients were compared with TAV patients [45,46] and patients with Marfan syndrome [47]. Moreover, Mohamed et al. showed that SMC isolated and grown in culture from convex and concave parts of the aortas of BAV patients were different in apoptotic behavior [48]. A local variability in the amount of eNOS protein expression, attributable to the local differences in shear stress, between aortas of patients with BAV and TAV has also been reported [49].

Our group has made several contributions that further highlight the differences in the molecular signature between patients with BAV and TAV in the process of aneurysm formation. Using 345 Affymetrix Exon arrays, we compared the expression profiles of aortic intima-media, aortic adventitia, and mammary artery from BAV and TAV patients, as well as aortic intima-media of transplant controls [50]. In summary, our data revealed that there was a small number of overlap of genes expressed in the dilated aorta of BAV and TAV patients although there were hundreds of differentially expressed genes associated with dilatation in BAV and TAV patients, signifying that molecular mechanism of dilation in BAV and TAV is largely different. In particular, the expression of immune response genes was higher in the dilated aortic media of TAV patients, implying a higher activation of immune response in dilatation of TAV but not BAV patients [50]. Relative lack of inflammatory signals in BAV compared to TAV aneurysms have been also reported by other researchers [51].

Analysis of alternative splicing of the TGFβ pathway mRNAs showed that BAV and TAV patients had different alternative splicing fingerprints following dilation, further supporting that the underlying mechanisms of aneurysm formation in BAV and TAV patients may be fundamentally different [52]. A comprehensive proteomic analysis of dilated aorta from BAV and TAV patients performed in our laboratory further confirmed that the dilated state of BAV and TAV aortic intima-media differed substantially also at protein expression level [53].

Reduced Tissue Repair in Patients with BAV?

We first discussed the notion of "defective repair" as a possible mechanism to explain the more disease prone aorta in BAV patients when Paloschi et al. showed that the aortic mRNA and protein expression of EDA splice variant of fibronectin, which is associated with wound healing [54], was up-regulated during aneurysm formation in TAV but not BAV patients [55]. Interestingly, a report comparing primary human aortic SMC lines found a reduced migration and a longer median time to the first passage for BAV SMCs relative to TAV and control SMCs, which was interpreted by the authors as slower process of tissue repair in BAV [56].

Furthermore, in another study we used a multistep filtering procedure termed "expression screening" to dissect flow mediated gene expression in BAV and TAV patients. The filtering procedure was based on a screening of a large collection of public microarray data sets for consistent coexpression with a set of well-characterized shear stress-regulated genes (query genes). Genes that coexpressed were selected and analyzed for coexpression with the query genes in an expression database consisting of array data from ascending aorta of BAV and TAV patients. To investigate the contribution of cuspidity versus other phenotypes, we used a multivariate analysis using dilation, stenosis, and regurgitation as covariates to cuspidity [57]. To summarize the result of this study, we demonstrated that: ***(i)*** important flow-induced genes such as KLF2, KLF4 and constituents of endothelial mechanosensory complex CDH5 and PECAM1 [58] were differentially expressed between BAV and TAV patients; ***(ii)*** a large number of identified flow-associated genes (~80%)

were associated with angiogenesis/wound healing related processes; and **(*iii*)** most of the angiogenesis-related genes were down-regulated in the aorta of BAV patients indicating an angiostatic profile. These observations, together with down regulation of inflammatory pathways in BAV relative to TAV, are in line with a slower repair process in BAV relative to TAV.

The Balance of Angiogenic Factors and its Role in Vascular Repair

Angiogenesis is the formation of new blood vessels, initiated by signals from the preexisting vascular endothelial cells. These signals modulate several growth factors and extracellular matrix components, as well as communication pathways between cell-cell and cell-matrix. The angiogenic modulators are not only capable of controlling angiogenesis but also regulating key functions of vascular cells, including proliferation, migration, and wound healing. A balance between angiogenic and angiostatic factors is critical for vascular tissue repair and homeostasis. It is, therefore, conceivable that maintenance of this balance is of crucial importance to the well-being of living organisms.

Aberrant angiogenesis has been implicated in several human diseases, including cancer, rheumatic arthritis [59], and preeclampsia [60]. Angiogenic factors are also essential for the development of embryonic cardiac valves and the perturbation in the regulatory mechanism of angiogenesis contributes to the development of cardiac valve diseases [61–63]. In the vasculature, the endothelium is the primary layer targeted by risk factors, and maintenance of a balance between endothelial injury and endothelial recovery is of fundamental importance to cardiovascular health. The repair of damaged vessels is intimately correlated with activation of angiogenesis and ECs have a key role in the initiation of this process.

Moreover, it is becoming increasingly clear that ECs are not only passive conduits for delivery of nutrients and oxygen. A hypothesis originally put forward by Rafii's group to explain tumor angiogenesis, proposes an "instructive" role for ECs through regulation of angiogenic factors, inflammatory cytokines and cell adhesion molecules, collectively called "angiocrines." Through the instructive expression of "angiocrines," ECs establish a particular vascular microenvironment or "niche" within which tumor angiogenesis and vascular repair can be promoted [64]. Regulation of angiocrines facilitates or prohibits the recruiting of stem cells and/or progenitor cells into the vascular niche to maintain vascular homeostasis.

During the last decade, the paradigm of the postnatal vasculature as a terminally differentiated tissue has been revisited following the discovery of diverse stem and progenitor cell populations in adult vessel walls. The original discovery by Asahara et al. [65] showed the existence of circulating endothelial progenitor cells (EPCs) and their role in neovascularization and since then a great deal of information has been accumulated on the role of EPCs, particularly in relation to cardiovascular disorders [66]. The origin and location of progenitor cells are still very controversial; there are reports on EPCs originating from hematopoietic lineage in bone marrow or from ECs circulating via blood or being resident in the vessels [67,68]. The consensus emerging from a recently published review is that major cell type involved in the repair of injured endothelium are the endogenous adjacent resident ECs within the vessels, and depending on the type of injury, they may cooperate with the proliferative circulating progenitor cells [67]. Although the tissue of origin still remains to be further clarified, highly proliferative progenitor cells have been recently identified both in human thoracic aorta [69] and in adult murine aortic tissues [70,71].

Taken together, one explanation for higher incidence of aortic complications in patients with BAV relative to patients with TAV may be the loss of balance between angiogenic and angiostatic factors affecting the repair mechanisms in BAV. The down regulation of the "angiocrines" in ascending aorta of patients with BAV could be a result of lower proliferative signal sent by the residence progenitor cells and a less attractive environment for the recruitment of circulating progenitors via lowered concentration of cellular adhesion molecules, making it an unsuitable vascular "niche" for repair. These ineffective repair processes would render the ascending aorta in BAV more fragile and more sensitive to local damage inflicted either by genetically inherited weakness in the wall or by chronic exposure to abnormal hemodynamics. Indeed ample evidence exists that hemodynamic factors are capable of regulating angiocrines and, hence, angiogenic balance of vascular niche [72–75]. Numerous in vitro and in vivo studies have established that shear stress can regulate the related processes, e.g., angiogenesis [75–78] proliferation and differenti-

ation of progenitor cells [79–84] and wound healing [85–90].

TGFβ and the Balance of Angiogenesis in Endothelium

In the aneurysm research community, the aberrant TGFβ signaling as a major contributor to aneurysm development is an established hypothesis. However, the discussion on the role of this pathway has largely been focused on SMCs and the fibroblasts, although TGFβ signaling also plays a crucial role in the maintenance of the intima layer and the defective signaling of this pathway in the endothelium may equally well contribute to aneurysms. Indeed, a recently published article reported that an endothelial specific mutation in angiotensin II type 1a (AT1a) receptor attenuated the angiotensin II (Ang II) induced ascending aortic aneurysm in mice [91] challenging the "media-focused" notion of vessel dilation.

The regulation of vascular endothelium by TGFβ is complex and contradictory and the mechanisms by which TGFβ regulates endothelial homeostasis and angiogenesis in vivo is not completely understood. At higher concentrations, TGFβ is inhibitory for EC proliferation and migration and angiogenesis, whereas at lower concentrations it is stimulatory. Several studies demonstrated a bifunctional mode of action for TGFβ in relation to ECs and angiogenesis, depending on the multiple choices of ligands binding to receptors. In ECs, TGFβ has been shown to signal via both the ubiquitously expressed type I receptor TGFβR1 (ALK5) and through the EC restricted receptor ACVRL1 (ALK1). Studies on signaling mechanisms initiated by ACVRL1 and TGFβR1 indicate a complex interaction between the receptors and their role in angiogenesis. In vitro and in vivo experiments demonstrated both pro [92] and anti angiogenic effects [93–95] for TGFβR1 and pro [94,96–98] and anti-angiogenic effects [99] for ACVRL1. Possible reasons for these contradictory results may be the different experimental conditions and contexts as well as dose dependency of TGFβ signaling. In spite of the inconsistencies, the emerging hypothesis is that a fine balance between ACVRL1 and TGFβR1 signaling regulates angiogenesis in endothelium. Depending on which type I receptor is recruited, different Smad signaling cascades are activated; ACVRL1 activation induces phosphorylation of Smad 1/5/8, whereas TGFβR1 leads to Smad 2/3 activation. The ACVRL1 stimulated expression of inhibitor of DNA binding 1 (ID1), promotes EC proliferation, migration, and tube formation, whereas TGFβR1 induces expression of plasminogen activator inhibitor1 (PAI1), which is a negative regulator of endothelial cell migration and angiogenesis. The final decision to embark on a pro- or anti-angiogenic pathway is determined by endoglin (ENG). Endoglin is an auxiliary receptor (TGFβRIII) for TGFβ family and in the vasculature is primarily expressed in proliferating ECs. Endoglin regulates the TGFβ-TGFβR1 and TGFβ-ACVRL1 signaling pathways negatively and positively, respectively, and this dual receptor system endows the ECs with a versatile mechanism for switching between different TGFβ-induced angiogenic responses. Another member of TGFβ ligand family, BMP9 also binds ACVRL1 and ENG and, interestingly, also shows a biphasic angiogenic response [100–103]. Importantly, the ACVRL1/TGFβR1 branch of the TGFβ pathway cross talks with other angiogenesis-related pathways such as VEGF [104,105], NOTCH [106], integrin α5 [105,107], and endothelial-specific adherens junction VE-cadherin [108] signaling.

Taken together, these observations may have relevance for aneurysm development in BAV. One conceivable scenario may be that the major target of aberrant TGFβ signaling in TAV aneurysm is the aortic media, while in BAV-associated aneurysms it is the intima layer and medial degeneration is only a secondary consequence. Indeed in BAV compared with TAV, we observed up regulation of TGFβR1 and down regulation of ACVRL1, ENG, ID1, ITGA5 (integrin α5), CDH5 (VE-cadherin), and VEGF family members, compatible with a TGFβ-dependent angiostatic profile [50, 57] unpublished observations). The emerging picture is also consistent with the crucial role of angiogenic balance in the development of cardiac valves as one can speculate that the balance between the two angiogenic branches of TGFβ pathway may explain the variation in the degree of aorthopathy observed among BAV patients. One point worth mentioning in this respect is that NOTCH1 that is associated with BAV inheritance in human is predominantly expressed in the vascular endothelium [109] and NOS3 (eNOS) that is mutated in the animal model of BAV is endothelial specific. Furthermore, a haplotype within the endoglin gene was found to be associated with BAV [110].

Undoubtedly, the available data on the interaction between the two TGFβ branches in the maintenance of an endothelial homeostatic state is anything but simple. This hypothesis is a simplified picture of a much more

intricate reality considering the context dependency of ligand-receptor interactions, concentration dependency as well as activation/inactivation of other pathways involved in a crosstalk with TGFβ [106]. However, this framework fits amazingly well with our observations as well as provides a context to ask more complicated questions. In addition, it accommodates both genetic and hemodynamic theories of aneurysm development in BAV. Although EC-specific genetic defects may result in aneurysm formation, many members of the TGFβ family, including TGFβ and BMP [111], TGFβR1 [112,113], ACVRL1 [114], and ENG [115], are shear stress responsive. Hence, lifetime exposure to abnormal hemodynamics is potentially capable of changing the angiogenic balance by increasing and decreasing the concentration and/or availability of different ligand-receptor combinations in a particular vascular niche in order to deteriorate the return to homeostasis, with or without an inherited weakness in the vessel wall.

Concluding Remarks

Disruption of aortic wall integrity in aneurysms is the outcome of a complex reciprocal interaction between different cell types within the aortic wall and between the aortic wall and the local environment. "Parsing Aortic Aneurysm: More Surprises" is the title of a recently published editorial commenting on the results of a report on EC-specific mutation leading to aneurysm formation in mice [116]. As we learn more about the many molecular mechanisms by which the cells relay signals to each other, it will perhaps be just the beginning of surprises. The role of endothelium in aneurysms adds yet another level of complexity to the tasks of TAA scholars. This entails a more flexible approach in the aneurysm research community for questioning dogmas. One issue that has not attracted much attention regarding aneurysm development is the role of the endothelium. The last decade has witnessed a change of trend in the field of aortic aneurysm from studying different patient cohorts to the discovery of cellular and molecular mechanisms underlying aortic wall degeneration. The next decade may be devoted to finding the fine molecular tuning underlying the communication between different cell layers in the aortic wall.

Adequate blood flow is the most important aspect of homeostasis in living organisms and angiogenesis is the most relevant process to maintain it. Hence, it is not surprising to discover an increasing number of human diseases being associated with the defective angiogenic signals. The endothelium senses all the changes, which may be carried and signaled by circulating media of blood flow, and the picture of endothelium as a passive conduit of oxygen and nutrients is changing as our knowledge of molecular features of signal transduction from intima to the other cell layers is expanding. The issues discussed in the present review may call for a paradigm shift from considering the aortic media being the prime target of aneurysmal degeneration to a further concentration on the intima layer, particularly in the development of aneurysm in BAVs. The clarification of the role of the endothelium may not only be important for molecular biologists but may also be of crucial interest to the medical community for the development of new therapies for the most common congenital cardiac disease of our time.

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EDITOR'S COMMENTS

In this thrilling review article, based on extensive work in his their own laboratory as well as the work of other groups, Eriksson and colleagues challenge us to think beyond current dogma regarding the genesis of thoracic aortic aneurysms, especially those that accompany bicuspid aortic valve. We must not have tunnel vision focused only on the media. Rather, say Eriksson and colleagues, we must consider the rich, complex endothelium as a potential major "player" in the genesis of aneurysm disease. A focus on the endothelium, the authors suggest, can permit integration of both genetic and hemodynamic forces in the genesis of aneurysms–taking us beyond the all-or-none, genes versus blood flow debate of the last several decades.