Canadian Journal of Cardiology 32 (2016) 13–25

Review

A Decade of Discovery in the Genetic Understanding of Thoracic Aortic Disease

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ABSTRACT

Aortic aneurysms are responsible for a significant number of all deaths in Western countries. In this review we provide a perspective on the important progress made over the past decade in the understanding of the genetics of this condition, with an emphasis on the more frequent forms of vascular smooth muscle and transforming growth factor β (TGF-β) signalling alterations. For several nonsyndromic and syndromic forms of thoracic aortic disease, a genetic basis has now been identified, with 3 main pathomechanisms that have emerged: perturbation of the TGF-β signalling pathway, disruption of the vascular smooth muscle cell (VSMC) contractile apparatus, and impairment of extracellular matrix synthesis. Because smooth muscle cells and proteins of the extracellular matrix directly regulate TGF-β signalling, this latter pathway emerges as a key component of thoracic aortic disease initiation and progression. These discoveries have revolutionized our understanding of thoracic aortic disease and provided inroads toward gene-specific stratification of treatment. Last, we outline how these genetic findings are translated into novel pharmaceutical approaches for thoracic aortic disease.

RÉSUMÉ

Les anévrismes de l'aorte sont responsables d'un nombre important de décès dans les pays occidentaux. Dans cette revue, nous avons mis en perspective le progrès important réalisé au cours de la dernière décennie en matière de compréhension de la génétique de cette affection et insistons sur les formes plus fréquentes de muscles lisses vasculaires et les détériorations de la signalisation du facteur de croissance transformant β (TGF-β : *transforming growth factor* β). Pour plusieurs formes syndromiques et non syndromiques de la maladie de l'aorte thoracique, nous avons maintenant établi le fondement génétique des 3 principaux pathomécanismes qui sont apparus : la perturbation de la voie de signalisation du TGF-β, la perturbation de l'appareil contractile des cellules musculaires lisses vasculaires (CMLV) et la dégradation de la synthèse de la matrice extracellulaire. Puisque les cellules musculaires lisses et les protéines de la matrice extracellulaire régulent directement la voie de signalisation du TGF-β, cette dernière apparaît comme une composante principale de l'apparition et de l'évolution de la maladie de l'aorte thoracique. Ces découvertes ont révolutionné notre compréhension de la maladie de l'aorte thoracique et ont permis des avancées dans la stratification de traitements visant des gènes particuliers. Enfin, nous soulignons comment ces découvertes génétiques entourant la maladie de l'aorte thoracique évoluent vers de nouvelles approches pharmaceutiques.

Thoracic aortic diseases (TAD) encompass dilation as well as aneurysms and dissections of the ascending or descending thoracic aorta. Population-based studies estimate an annual incidence of 6-16 cases per 100,000, and aortic dissection is the most devastating complication of TAD.[1,2] Results of clinical studies have long suggested a familial predisposition for TAD, and it has been estimated that 20% of cases are caused by genetic factors.[3-5] In addition to the better known entity of Marfan syndrome (MFS), a multitude of novel causal genes has been identified for TAD at an ever-accelerating pace over the past decade, so that it is difficult even for the interested reader to keep abreast with the more recent developments and controversies. The focus of this review therefore is on providing, in sequence and context, a primer on where the most important lines of research in TAD over the past decade have come from and what progress has been made in recent years. Finally, we will discuss implications for clinical care and research, now and in the years to come.

Received for publication September 1, 2015. Accepted October 18, 2015.

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See page 20 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.10.017

Historical Context

Although the first descriptions of aneurysms date back to antiquity, it was not until the Renaissance and its novel view of man and human anatomy that a more detailed understanding of aneurysms started to develop (timeline in Table 1 and Suy[6]). With Antoine Marfan's seminal observation of the first case of the disease, which is now named after him, in 1896, and the realization that aortic disease is part of this entity in 1912, the first syndromic form of TAD became apparent.[7,8] In 1955, McKusick provided the first larger case series and characterized the cardiovascular phenotype of MFS and suggested that MFS is a heritable monogenic disorder.[8,9] Since the discovery of fibrillin-1 (*FBN1*) as the causal gene in MFS,[10] the phenotypic and genetic spectrum of TAD has vastly expanded. Study of the syndromic forms of human TAD has now identified the transforming growth factor β (TGF-β) pathway as a key driver in disease pathogenesis and progression, whereas in nonsyndromic TAD mutations in other diverse genes prevail.

Insights From MFS: Dead Ends and Inroads in Fibrillogenesis

Among the earlier studies on the histopathology of MFS, it was noted that the thoracic aorta of Marfan patients exhibits changes similar to cystic medianecrosis—now called more appropriately medial degeneration—as well as altered collagen and elastic fibre content and architecture.[11-15] These and other studies suggested that in MFS, tropoelastin deposition and collagen crosslinking were altered during embryogenesis and early postnatal life. Aortic dilation and aneurysm in MFS was thus explained mainly as a scaffolding defect, in which elastic fibre maturation was disrupted by defective microfibrillar assembly. This initial focus, however, was not compatible with several observations in diseases marked by elastin deficiency. Although humans have multiple paralogs for numerous genes that constitute the extracellular matrix—such as for collagens—there is only 1 elastin gene in the human genome. Williams-Beuren syndrome, a rare developmental disorder caused by a microdeletion that encompasses elastin, is characterized by supravalvular stenosis of the great arteries, in particular the aorta, and not aortic dilation.[16,17] Similarly, the predominant phenotype in point mutations in the elastin gene also is supravalvular aortic stenosis.[18] Compatible with these observations, mutations in several genes known to drive elastic fibre formation and their associated disorders—such as in fibulin (*FBLN*)-5 (*FBLN5,* cutis laxa type IA), the transmembrane transporter *ABCC6* (generalized arterial calcification; pseudoxanthoma elasticum), and latent TGF-β binding protein 4 (cutis laxa type IC)— do not go along with aortic aneurysm.[19-22] However, mutations in *FBLN4* (cutis laxa type IB), another regulator of elastogenesis, are characterized by a high incidence of aortic aneurysms, arterial tortuosity, and stenosis.[23] Still better described are the numerous ultrastructural changes of the extracellular matrix in MFS, mainly disrupted and thickened elastic lamellae, and accumulation of extracellular glycosaminoglycan-rich material.[24] Taken together, these observations clearly show that seemingly similar genetic defects can lead to drastically different phenotypes, and that defective elastogenesis per se is very unlikely to be the prime driver of aortic dilation. It is conceivable that divergent interaction partners of *FBLN4* vs *FBLN5* or differing cell-lineage requirements for these factors are decisive in these binary outcomes.[25]

If purely mechanical consequences did not explain tissue failure in MFS, what other roles could extracellular matrix proteins play then? Initial sequence analysis had already provided evidence that *FBN1* had several regions of structural homology with latent TGF-β binding proteins, which was followed by experimental evidence that these proteins interact to fine-tune TGF-β signalling and the recognition that growth factor dysregulation plays an important role in diseases caused by fibrillin mutations.[26-29] Animal models then provided crucial clues for further dissection of the consequences of mutations of extracellular matrix proteins, in particular *FBN1*.[30] Of particular importance, analysis of the lung phenotype in a *Fbn1*-deficient mouse model with emphysema showed that anomalies of alveolar septation were already present at birth and predisposed to destructive emphysema at later age.[31] At the molecular

Table 1. A brief summary of selected time points that are important for our historical and current understanding of the anatomy and pathogenesis of TAD

Year	Author	Finding	Reference
1554	Vesalius	Anatomy of man ('De Humani Corporis Fabrica') Proper understanding of aortic morphology	172
1585	Paré	Attributed aneurysms to syphilis, hard work, shouting, trumpet-playing, and childbirth	173
1767	Morgagni	Described in detail the pathology of aortic aneurysm secondary to syphilis	174
1733	Monro	Described the intima, media, and adventitia of arterial walls	175
1750s	Hunter brothers	Modern definitions of true, false, and mixed aneurysms	6
1761	Nicholls	Death of King George II attributed to aneurysm rupture	176
1896	Marfan	Description of Marfan syndrome	7
1912	Salle	Aortic pathology as part of Marfan syndrome	8
1943	Baer et al.	Recognition of histopathological changes in the aorta of Marfan patients	11
1955	McKusick	Characterization of cardiovascular phenotype of Marfan syndrome	9
1986	Sakai et al.	Discovery of fibrillin	177
1991	Dietz et al.	Identification of fibrillin-1 mutations as a cause of Marfan syndrome	10
2004	Cripe et al.	Quantification of the heritability of bicuspid aortic valve and associated malformations	105
2005 to present	Loeys, Dietz, and others	Identification of several TGF-β-driven syndromes Identification of angiotensin receptor blockade as therapeutic concept in mice	32,34,77
2006 to present	Milewicz and others	Identification of the contractile apparatus of the vascular smooth muscle cell as a driver of TAD	85-87
2014	Pediatric Heart Network	Results of prospective randomized trial in Marfan syndrome	154

TAD, thoracic aortic diseases; TGF, transforming growth factor.