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Review

Structure of the Elastin-Contractile Units in the Thoracic Aorta and How Genes That Cause Thoracic Aortic Aneurysms and Dissections Disrupt This Structure

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ABSTRACT

The medial layer of the aorta confers elasticity and strength to the aortic wall and is composed of alternating layers of smooth muscle cells (SMCs) and elastic fibres. The SMC elastin-contractile unit is a structural unit that links the elastin fibres to the SMCs and is characterized by the following: (1) layers of elastin fibres that are surrounded by microfibrils; (2) microfibrils that bind to the integrin receptors in focal adhesions on the cell surface of the SMCs; and (3) SMC contractile filaments that are linked to the focal adhesions on the inner side of the membrane. The genes that are altered to cause thoracic aortic aneurysms and aortic dissections encode proteins involved in the structure or function of the SMC elastin-contractile unit. Included in this gene list are the genes encoding protein that are structural components of elastin fibres and microfibrils, *FBN1*, *MFAP5*, *ELN*, and *FBLN4*. Also included are genes that encode structural proteins in the SMC contractile unit, including *ACTA2*, which encodes SMC-specific α-actin and *MYH11*, which encodes SMC-specific myosin heavy chain, along with *MYLK* and *PRKG1*, which encode kinases that control SMC contraction. Finally, mutations in the gene encoding the protein linking integrin receptors to the contractile filaments, *FLNA*, also predispose to thoracic aortic disease. Thus, these data suggest that functional SMC elastin-contractile units are important for maintaining the structural integrity of the aorta.

RÉSUMÉ

La tunique moyenne de l'aorte qui confère l'élasticité et la force à la paroi aortique est composée de couches alternantes de cellules musculaires lisses (CML) et de fibres élastiques. L'unité contractile-élastine CML qui est une unité structurale liant les fibres d'élastine aux CML est caractérisée par ce qui suit : 1) les couches des fibres d'élastine qui sont entourées de microfibrilles; 2) les microfibrilles qui se lient aux récepteurs de l'intégrine dans les adhérences focales de la surface des CML; 3) les filaments contractiles des CML qui sont liés aux adhérences focales de la face interne de la membrane. Les gènes qui sont altérés pour causer les anévrismes de l'aorte thoracique et les dissections aortiques encodent les protéines impliquées dans la structure ou le fonctionnement de l'unité contractile-élastine CML. Les gènes qui sont inclus dans cette liste sont les gènes encodant les protéines qui sont les composantes structurales des fibres d'élastine et des microfibrilles, le gène *FBN1*, le gène *MFAP5*, l'*ELN* et la *FBLN4*. Les gènes qui sont également inclus sont les gènes qui encodent les protéines structurales de l'unité contractile des CML, dont le gène *ACTA2*, qui encode l'actine α des CML et le gène *MYH11*, qui encode la chaîne lourde de la myosine des CML, ainsi que les gènes *MYLK* et *PRKG1*, qui encodent les kinases régulant la contraction des CML. Finalement, les mutations du gène encodant la protéine qui lie les récepteurs de l'intégrine aux filaments contractiles, le *FLNA*, prédisposent également aux maladies de l'aorte thoracique. Par conséquent, les présentes données suggèrent que les unités contractiles-élastine CML fonctionnelles sont importantes pour maintenir l'intégrité structurale de l'aorte.

The term "arterial aneurysm" was used in the Ebers Papyrus writings of ancient Egyptians in 2000 BC.[1] Four millennia later, our understanding of the pathophysiology of aortic aneurysm is far more complex than simple enlargement of the vessel diameter. There have been tremendous strides in understanding the pathophysiology, diagnosis, and treatment of this deadly disease. The natural history of an aneurysm that involves the root or the ascending thoracic aorta or both (ie, a fusiform aneurysm) is progressive, asymptomatic enlargement over time. In the absence of surgical repair of the aneurysm, the progressive enlargement can lead to an acute ascending (type A) aortic dissection. Although medical treatments can slow the rate of enlargement of an aneurysm, the mainstay of treatment is pre-emptive surgical repair of the thoracic aortic aneurysm before the occurrence of dissection or rupture. This repair is typically recommended when the aneurysm's

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diameter reaches 5.0-5.5 cm; however, studies on patients who presented with acute type A dissections indicate that up to 60% present with aortic diameters smaller than 5.5 cm.[2] Therefore, clinical predictors are needed to identify those at risk for type A aortic aneurysm or dissection (TAAD) and determine the aortic diameter that justifies the risk of surgical repair of a thoracic aortic aneurysm to prevent acute aortic dissection or rupture. We and others have established that identification of a disease-causing mutation in a specific gene can identify who else is at risk for TAAD in the family and predict at what range of aortic diameters a dissection will occur, and thereby optimize the timing of aortic surgery to prevent dissections.[3,4]

The aortic wall is composed of 3 layers. The tunica intima (the innermost layer) is composed of a single layer of endothelial cells and is supported by the internal elastic lamina. The thick tunica media (the middle layer) is composed of > 50 alternating layers of elastic lamellae and smooth muscle cells (SMCs). Elastin fibres are composed of a core of elastin surrounded by microfibrils and it is the microfibrils that link to the SMCs through focal adhesions (also called dense plaques) on the cell surface of SMCs. Inside the SMC, the contractile units also link to the focal adhesions. The elastin-contractile unit is the functional and structural unit of the tunica media that will be discussed in detail in this review. Finally, the tunica adventitia (the outermost layer) is mainly composed of collagen and contains the vasa vasorum (small arteries that supply nutrients to the medial layer) and autonomic nerves.

The aorta has a unique role in blood flow because it acts as an elastic buffering chamber for the heart, termed the Windkessel function. The aorta and some of the proximal large vessels store approximately 50% of the left ventricular stroke volume during systole. Then, in diastole, the elastic forces of the aortic wall push this volume forward to the peripheral circulation, and thus creates a nearly continuous peripheral blood flow. This elastic buffering capacity is because of the elastin in the aortic wall and not because of the contraction of the SMCs. If the SMC contraction is pharmacologically inhibited, the elastic recoil of the aorta does not change.

The pathologic changes in the medial layer of patients with an acute aortic dissection were first described by Babes and Mironescu in 1910,[5] and the term "cystic medial necrosis" was later coined as the pathological hallmark of TAAD by Erdheim in 1929.[6] "Cystic medial necrosis" is a misnomer because the pathology associated with TAAD has no cyst formation or overt necrosis. Instead, TAAD is characterized by fragmentation and loss of elastic fibres, accumulation of proteoglycans, and loss of SMCs. Some studies have shown hyperplastic cellular remodelling in the aortic media as an aneurysm enlarges, such that there is no reduction of the total number of SMCs in the aorta, but there are often focal areas of SMC loss in the medial layer.[7] Immunohistochemical studies have shown significantly higher presence of $CD3^+$ (a T-cell marker) and $CD68^+$ (a monocyte and/or macrophage marker) in ascending aortic aneurysms compared with normal aortas, but the role of inflammation in the pathogenesis of TAAD has not been firmly established.[8]

In this review, we examine the normal structure of the thoracic aorta and the role of mechanotransduction in development and homeostasis of the aortic wall. In addition, how the gene alterations that predispose to TAAD disrupt components of the elastin-contractile unit will also be discussed.

SMC Contractile Unit and Mechanotransduction

The elastin-contractile unit is a functional and structural unit in the aortic media, which provides a direct connection between the SMC and the elastin fibres.[9] On the basis of the genes that cause thoracic aortic disease, this interaction is pivotal for maintenance of the integrity of the thoracic aortic wall. The elastic fibres are organized in concentric laminae, and the core of elastin is surrounded by microfibrils. These microfibrils are 10-15 nm filaments composed primarily of a large glycoprotein called fibrillin (encoded by *FBN1*, *FBN2*, and *FBN3*). There are additional microfibril-associated glycoproteins (MAGPs), including MAGP-1 and MAGP-2 (encoded by *MFAP2* and *MFAP5*, respectively), and elastin microfibril interfacer protein 1 (EMILIN1) encoded by *EMILIN1*. The elastin and microfibrils form extensions that are organized in an oblique orientation to the elastic fibres, and are attached to the dense plaques in the SMC cell membrane (Figs. 1 and 2). The SMCs are longitudinally

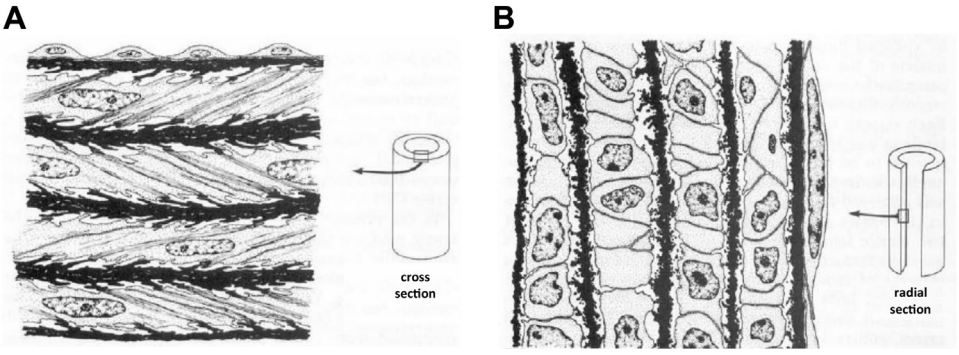

Figure 1. Schematic representations of cross-sections of the aorta showing the relationship between the elastin lamellae and the smooth muscle cells (SMCs). (**A**) The elastic lamellae are depicted as the **black layers** and the SMCs are shown between elastic lamellae. The elastin has oblique extensions that connect with the surface of the SMCs at focal adhesions (also called dense plaques). The smooth muscle α-actin filaments attach to the membrane at these focal adhesions and extend obliquely across the cell. The direction of these oblique extensions changes from layer to layer. (**B**) The SMCs are shown in cross-section between the elastin lamellae. The elastin extensions to the SMCs are viewed in cross-section at the edge of the elastic lamellae and give the elastin fibres an irregular appearance. Reproduced with permission from Davis.[9]