Heterogeneity of aortic smooth muscle cells: A determinant for regional characteristics of thoracic aortic aneurysms?

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INTRODUCTION

Thoracic aortic aneurysm (TAA) is defined as a permanent dilation of the thoracic aorta that is associated with a propensity for rupture and dissection. The general term of TAA covers the manifestation of aortic dilation that occurs in a wide range of syndromic and non-syndromic conditions. Within these conditions, aortic pathologies manifest in distinct regions of the thoracic aorta.

Smooth muscle cells (SMCs) are the only cell type resident in the normal aortic media and are crucial in maintaining aortic wall integrity. The functional properties of SMCs, such as contractility and proliferation, are different in each aortic region and may contribute to the pathophysiology of TAA. SMCs in the thoracic aorta are heterogeneous in their embryologic origin.[1] It has been inferred that the different embryonic origins may have functional difference, although this has not been defined in the context of TAA development. This editorial summarizes recent publications that implicate embryonic origins of SMCs that are responsible for the regional characteristics of TAAs.

REGION-SPECIFIC FEATURES OF TAAS

The thoracic aorta is composed of four distinct regions: aortic root, ascending aorta, aortic arch, and descending portion.[2] Of note, 60% of TAAs impact the aortic root and/or the ascending aorta in human.[3] For example, TAAs in Marfan syndrome and Ehlers-Danlos syndrome occur most often in the aortic root.[4-6] TAAs in Loeys-Dietz syndrome and Turner syndrome preferentially form in both the aortic root and the ascending aorta.[7-10] Aortic aneurysms in patients with bicuspid aortic valve are most commonly reported in the ascending aorta.[11] This regional specificity extends to inflammatory TAA as well; syphilis and Takayasu arteritis mainly affect the ascending aorta.[12,13] Thus, the wide range of aortic root and ascending aortic aneurysm pathologies suggests that these two regions are more susceptible to aortic pathologies.

This distinct regional distribution is also observed in multiple TAA mouse models. Fibrillin 1 haploinsufficient (fibrillin 1[C1041G/+]) mice and hypomorphic (fibrillin 1[mgR/mgR]) mice are commonly used Marfan syndrome mouse models. Both models exhibit aortic root and ascending aortic dilation.[14-19] Mice with postnatal deletion of TGF-β receptor 1 or 2 in SMCs that mimic Loeys-Dietz syndrome develop aneurysms spanning from the aortic root to the descending aorta.[7, 20-23] In a non-syndromic TAA mouse model, chronic infusion with angiotensin II (AngII) leads to the formation of TAAs that are restricted to the ascending aortic region.[24, 25] Mechanisms driving this regional specificity of TAAs in human and mouse have not been defined.

SMC FUNCTIONS IN TAAS

SMC functions, including contractility and proliferation, play a pivotal role in aortic homeostasis and vary in different aortic regions. However, the potential impact of these functions on the regional specificity of TAAs has not been defined. AngII promotes aortic contraction but only in the infrarenal region of the mouse aorta.[26] In addition, chronic infusion of AngII induces medial hyperplasia of the ascending aorta but hypertrophy in the other aortic regions.[27] Furthermore, SMCs in the ascending aorta are more susceptible to TGF-β1-induced cell proliferation compared to SMCs in the abdominal aorta.[28] These functional differences may be associated with the pathophysiology of TAAs.

In human TAA tissues, the expression of a marker of SMCs, α-smooth muscle actin, is decreased.[21,22] Interestingly, this expression shows a gradient that decreases from the luminal to the adventitial aspects of the media. Simultaneously, proteoglycan deposition, a marker of extracellular matrix remodeling, occurs predominantly in the adventitial aspect of the media. In addition, aortic dissection, a disease characterized by the creation of a false channel within the aortic media, preferentially occurs in the outer third of the aortic media.[29] Aneurysmal tissue from TAA mouse models also exhibits a gradient of medial pathologies that is consistent with human TAA features. For example, Marfan syndrome mouse models (fibrillin 1[C1041G/+] and fibrillin 1[mgR/mgR]), Loeys-Dietz syndrome mouse models (TGF-β receptor 1 or 2 deletion in SMCs), and the AngII-induced TAA mouse models exhibit prominent medial pathologies such as medial thickening and elastin fragmentation that preferentially forms in the outer medial aspect (Figure 1).[19-25, 30] Thus, medial pathologies show a gradient toward the outer medial aspect in human and mouse TAAs.

EMBRYONIC ORIGINS OF SMCS IN THE THORACIC AORTA

Using mice with lineage tracing constructs, recent publications have delineated the heterogeneous embryologic origins of SMCs within the thoracic aorta. SMCs in the thoracic aorta are derived from three different embryonic origins: the cardiac neural crest (CNC), the second heart field (SHF), and the somites (Figure 2A).[1, 31-33] The CNC originates from the ectoderm, and CNC-derived SMCs are expressed from the aortic root to the end of the aortic arch.[32-34] The SHF is derived from the pharyngeal arches of the mesoderm, and SHF-derived cells are expressed from the aortic root to the branch of the innominate artery.[33, 35, 36] The CNC and SHF interact with each other
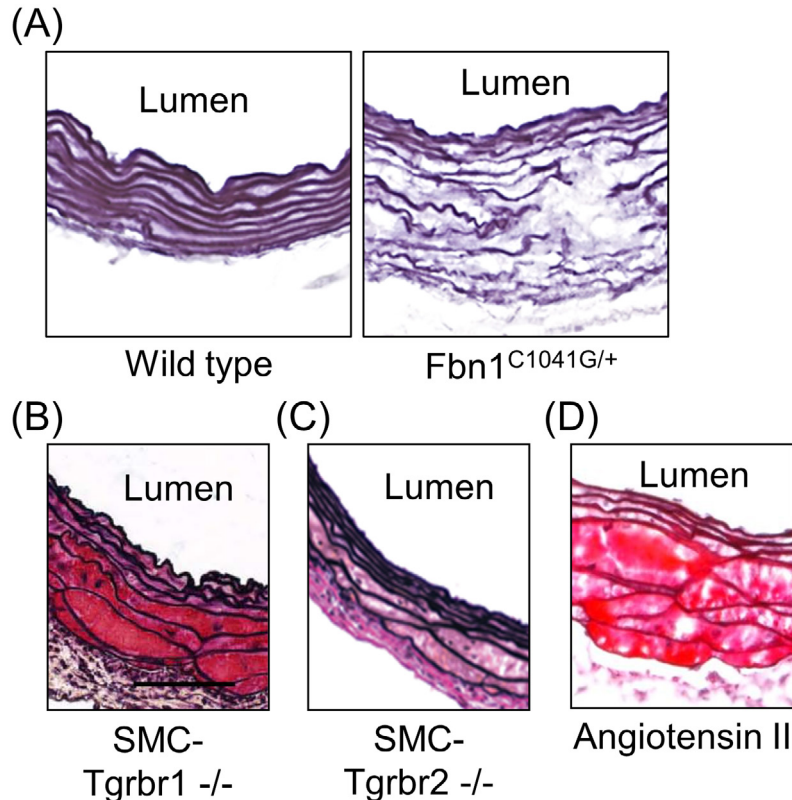

(A)

Wild type   Fbn1[C1041G/+]

(B)   **(C)**   **(D)**

SMC-Tgrbr1 -/-   SMC-Tgrbr2 -/-   Angiotensin II

Figure 1: Representative ascending aortic images of (A) wild type and fibrillin1 [C1041G/+] mice,[19] (B) SMC-specific TGF-β receptor 1 deleted mice,[23] (C) SMC-specific TGF-β receptor 2 deleted mice,[22] and (D) angiotensin II-infused mice.[25]
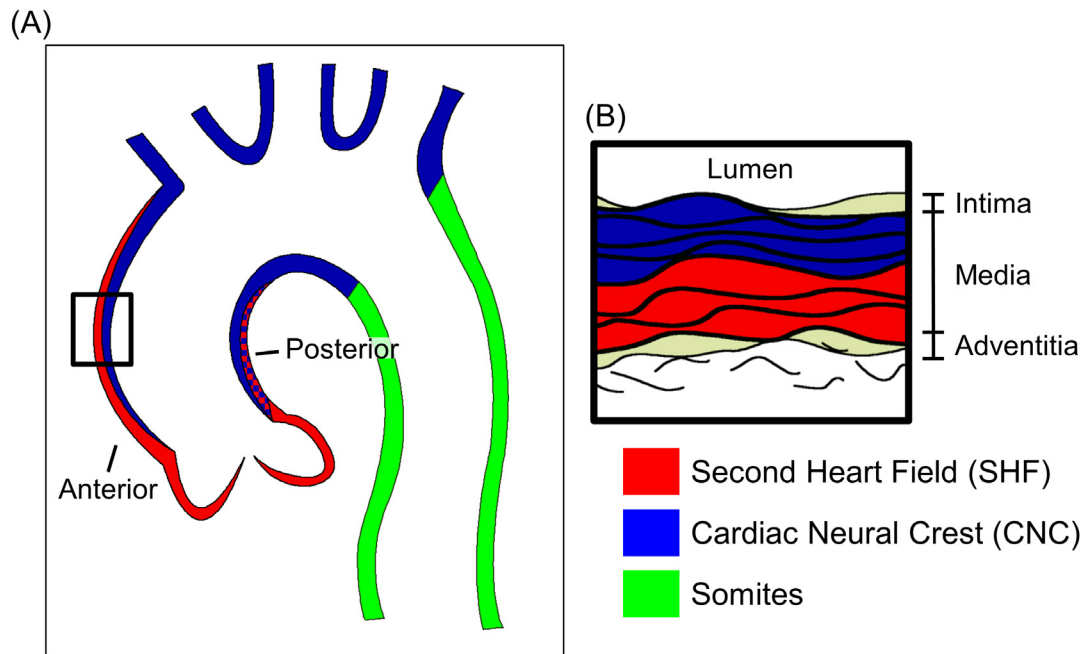
Figure 2: (A) Schematic illustration of embryonic origins of SMCs in the thoracic aorta. (B) Magnified image is captured from the black box. Blue, red, and green in the images indicate CNC-, SHF-, and somite-derived cells, respectively.

and are essential for the development of the ascending aorta.[37] The descending aorta is derived from the somites, which are formed from the paraxial mesoderm.[38-40]

Although SMCs of the aortic arch and descending aorta are derived from a single origin, the ascending aorta contains overlapping SMCs from both CNC and SHF origins. An SMC lineage tracing study has discovered that CNC- and SHF-derived SMCs in the ascending aorta show a spatially distinct distribution (Figure 2B).[33] CNC-derived SMCs reside in the inner medial aspect of the anterior portion and in the transmedia of the posterior portion of the ascending aorta. Conversely, SHF-derived SMCs locate in the outer medial layers of both the anterior and posterior portions. Thus, the outer medial SMCs of the ascending aorta form a sleeve populated by SHF-derived SMCs, which is coincident with medial pathologies.

The regional specificity and medial gradient of aortic pathology in TAAs correspond to the distribution of embryologic origin of SMCs. In addition, the functional properties of SMCs are different in different aortic regions. Thus, SMCs of different embryonic origins may have different functions that affect the pathophysiology of TAAs. While the proximal thoracic aorta of chicken and mouse is populated with SMCs of these embryonic origins, it is unknown whether this specific pattern of CNC and SHF origins is present in humans. Further studies that define CNC and SHF origins in postnatal tissue to determine whether human tissue is populated with SMCs of these origins are needed.

CONCLUSION

TAA formation exhibits regional specificity, which is also characterized by pathologic changes in the outer medial layers of the aorta. The distinct embryonic origins of SMCs in the thoracic aorta may explain these specific pathologic features. This is one facet of the many unknown features in the mechanisms of TAAs.

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Conflict of Interest
None declared.

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