Editorial

Challenges in thoracic aortic aneurysm and dissection

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Thoracic aortic aneurysm (TAA) and dissection (TAD)

TAA and TAD are serious clinical conditions that can result in fatal outcome (1). TAA is a chronic and local dilation of thoracic aorta. TAA itself presents no clinical symptoms unless it oppresses neighboring organs as a space occupying lesion. However, TAA grows over the time and eventually ruptures, frequently resulting in sudden death. On the other hand, TAD occurs suddenly without preceding clinical signs or symptoms with abrupt and severe chest or back pain. TAD is caused by the tearing of the intimal-medial complex perpendicular to the aortic wall thickness, followed by the longitudinal tearing of the medial layer. Despite the advances in the medical science and clinical practice, the challenges remain tough for TAA and TAD because their disease mechanisms are still incompletely understood.

The diagnostic challenges in TAA are the initial diagnosis for the presence of TAA as it usually does not present clinical signs or symptoms, the prediction of TAA growth after the initial diagnosis, and ultimately the prediction of TAA rupture. The therapeutic challenge in TAA is the prevention of TAA growth and rupture, which is currently achieved only by surgical replacement of the diseased aorta either by open surgery or endovascular insertion of the stent-graft. Therefore, discovery and development are much awaited for the diagnostic biomarkers for the presence of TAA, the prediction biomarkers and therapeutic target for TAA growth and rupture.

Challenges for the clinical management for TAD is different from those for TAA due to the different clinical manifestations. Because TAD develops usually with severe pain, recognizing the presence of serious clinical condition is not a problem. However, differentiating TAD from other serious diseases, such as myocardial infarction, can be problematic especially in a situation where advanced clinical imaging modalities, such as computed tomography and magnetic resonance imaging, are not readily available. Once diagnosed, the therapeutic option for TAD depends on the location of the cavity formed by the longitudinal medial tearing, termed as a false lumen. Emergency surgery is the first option for TAD involving ascending aorta (classified as Stanford type A). Stabilization of the diseased aorta by complete rest and lowering blood pressure is the first option for TAD without the involvement of ascending aorta (classified as Stanford type B). For those who survived the acute phase of TAD, either Stanford type A or B, the problem is the damaged aorta. Because of the aortic tissue damage and adverse remodeling, recurrence of TAD, aortic aneurysm formation and distal ischemia due to the occlusion of arterial blanches can occur in the chronic phase. Therefore, the clinical needs are the identification of biomarkers for the initial diagnosis that can differentiate TAD from other serious conditions, the prediction markers for the fragility and adverse remodeling of the aorta, and therapeutic targets for the acute or chronic stabilization of the damaged aorta. In addition, it would be ideal if one can predict the TAD development with confidence and prevent the TAD development, although theoretical basis for these goals is currently far less than sufficient.

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Insight from familial monogenic thoracic aortic aneurysm and dissection (TAAD)

Although clinical manifestations are quite different between TAA and TAD, they seem to have something in common in their pathogenesis. Dilated aorta due to TAA is more prone to TAD, possibly due to the increase in the aortic wall tension with a given aortic pressure according to Laplace's law. In addition, a group of monogenic hereditary diseases, collectively known as familial TAAD, has been recognized to manifest both TAA and TAD (2). Importantly, the patients of familial TAAD can develop TAD without significant dilation of the aorta, indicating that the dissection is not solely due to the physical stress due to the abnormal geometry of the aorta.

The prototypical clinical entity of TAAD is Marfan syndrome that is caused by mutations of FBN1encoding the extracellular matrix (ECM) protein Fibrillin-1. Mutations of genes encoding collagens, another type of ECM proteins, including COL1A2, COL3A1, COL5A1 and COL5A2, are known to cause Ehlers-Danlos syndrome (EDS), and some of EDS manifests familial TAAD. These familial TAAD diseases implies the importance of ECM in the homeostasis of aortic tissue to tolerate the hemodynamic stress. This concept is supported by the fact that mutations of genes encoding transforming growth factor β (TGF-β) pathway molecules, including TGF-β2, TGF-β3, their receptors and the downstream intracellular mediators SMAD2, SMAD3 and SMAD4, also cause familial TAAD, collectively known as Loeys-Dietz syndrome. Because TGF-β pathway governs ECM metabolism (3), its abnormality would have profound impact on the aortic homeostasis and can explain the common clinical manifestation of TAAD for both ECM and TGF-β pathway mutations.

Another important piece of the puzzle of aortic pathology is smooth muscle cells (SMCs) that regulate the integrity of aortic wall by their contraction/relaxation and ECM metabolism. The importance of SMCs is evidenced by the fact that mutations in SMC-specific genes also manifest TAAD phenotype. Those SMC-specific genes include ACTA2, MYH11, and MYLK that encode smooth muscle α-actin, SMC-specific isoform of myosin heavy chain, and myosin light chain kinase, respectively. Of note, these proteins work in concert to regulate the vascular tone by the function of actomyosin motor proteins, suggesting the dynamic regulation of aortic wall tone is important for the maintenance of the aortic tissue integrity. Another cause of familial TAAD is the gain-of-function mutation of PRKG1, which encodes cGMP-dependent protein kinase. Activation of cGMP-dependent protein kinase results in the relaxation of SMCs, underscoring the importance of SMC contractility in maintaining the integrity of aortic walls. Although genetic evidence clearly indicates the importance of ECM, TGF-β and SMCs, how these pieces of the puzzle are put together to form the maintenance mechanism of the aortic tissue mechanism, or how the abnormality of the mechanism leads to TAAD phenotype is largely unknown.

Molecular mechanism of TAAD

Recent studies have uncovered a part of the mechanism and molecules that participate in the mechanism in mouse models of TAAD. These molecules include ECM proteins Fbn1 (4), Col1a1 (5), Col3a1 (6), biglycan (7), tenascin C (8) and fibulin-4 (9), and molecules in TGF-β pathway (10,11), underscoring the importance of ECM metabolism in the tissue integrity of aorta. The importance of SMCs is also shown by the fact that smooth muscle-specific deficiency of Sirtuin-1 (12) or Akt2 (13) confers susceptibility to TAAD in mice. Abnormal aortic tissue integrity and aortic stress seem to culminate in proinflammatory response and tissue destruction, involving macrophage Socs3 (14), Nlpr3 (15), GM-CSF (16), CXCL1, G-CSF (17), Nox1 (18), IL-6, Mcp1 (19) and MMP-9 (20).

Recently, a new molecule SmgGDS, also known as Rap1GDS1, has been added to the group of smooth muscle proteins that participate in TAAD pathogenesis (21). As its name implies, SmgGDS is a GDP dissociation stimulator (GDS) for small GTPases. Small GTPases are a family of more than 100 proteins that regulate almost all aspects of cellular physiology. Small GTPases share the common protein structure that catalyzes guanine triphosphate (GTP) to guanine diphosphate (GDP) and inorganic phosphate, which is associated with the changes in the protein structure, resulting in the switching of their ability to bind to partner proteins between the GDP-bound "off" state and GTP-bound "on" state. The exchange of GDP to GTP turns the GTPase to "on" state, which is catalyzed by a group of molecules, termed as guanine nucleotide exchange factor (GEF) or GDS, to which SmgGDS belongs. After the GDP/GTP exchange, GTP is hydrolyzed to GDP by the intrinsic activity of GTPase, thus returning to the "off" state. In addition to the GEF activity, SmgGDS also regulates prenylation, a critical post-translational modification of GTPases for their function, and intracellular localization of GTPases. SmgGDS as a

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GEF regulates multiple small GTPases, including RhoA, RhoB, RhoC, Rac1, Rac1, Rap1A, Rap1B, K-Ras and CDC42. Because of the multiple target GTPases and the multiple functions, the physiological and pathophysiological roles of SmgGDS are likely diverse.

Nogi *et al.* investigated the role of SmgGDS in the context of aortic pathology by comparing the phenotype between wild type and heterozygous knockout of SmgGDS in the background of hyperlipidemic Apoe$^{-/-}$ background. It is widely accepted that continuous infusion of angiotensin II in Apoe$^{-/-}$ mice causes aneurysm and dissection in thoracic and abdominal aorta (22,23). In this murine model of aortic diseases, heterozygous deletion of SmgGDS resulted in worsened aortic destruction and rupture in thoracic aorta but not in abdominal aorta. This phenotype indicates that SmgGDS is involved in the tissue protection from the angiotensin II-induced destruction specifically in thoracic aorta, although exactly how the mechanism for this localized protection remains to be elucidated. Consistent with the reported function of SmgGDS, activities of RhoA, RhoC and Rap1 were reduced in SmgGDS$^{+/-}$:Apoe$^{-/-}$ aorta compared to SmgGDS$^{+/+}$:Apoe$^{-/-}$ aorta. Of note, expressions of familial TAAD culprit genes Fbn1, Acta2, Mylk, Myh11 and Prkg were also reduced in the same context. In addition, expressions of NADPH oxidase components and production of reactive oxygen species, MMP9 that degrades ECM, inflammatory signaling molecules including cyclophilin A and TGF-β signaling molecules were misregulated in SmgGDS$^{+/-}$:Apoe$^{-/-}$ aorta toward the TAAD-prone phenotype that recapitulate the familial TAAD diseases in human. Therefore, SmgGDS is likely to maintain the destruction-resistant phenotype of the aortic tissue. This notion was further supported by the gene transfer experiments that exogenously added SmgGDS rescued the TAAD-prone phenotype of SmgGDS$^{+/-}$:Apoe$^{-/-}$ mice. Because bone marrow transplantation experiments demonstrated that the protective function of SmgGDS was achieved not in bone marrow-derived cells but in aortic tissue resident cells, the authors focused on the function of SmgGDS in vascular SMCs, the main constituent of the aortic walls. Through a series of experiments, the authors convincingly showed that SmgGDS plays a critical role in SMCs for mechanosensing of cellular stretch and chemosensing of AngII. These finding may be relevant with human TAAD, because expression of SmgGDS was reduced in human TAAD tissue compared to normal aorta, and AngII reduced expressions of SmgGDS and ACTA2 only in TAA-derived aortic SMCs, not in those derived from non-TAA aorta.

TAAD as a "network" disease

Familial monogenic TAADs have provided important clues for the role of ECM, TGF-β signaling and SMCs-specific molecules in the homeostasis of aortic walls. However, it remains a mystery whether these factors are related to each other in the maintenance of aortic wall integrity, or whether and how they are involved in pathogenesis of non-familial TAAD. The elegant work by Nogi *et al.* has provided part of the answers to these questions. Genetic modification of SmgGDS resulted in the changes in all of ECM, TGF-β signaling and SMC phenotypes, indicating that these factors are likely to work in concert at least in the mouse model of TAAD and possibly in human TAAD as well. In other words, a network involving ECM, TGF-β signaling and SMC-specific molecules may maintain the integrity of aortic walls in the fluctuation of hemodynamic and neurohumoral environment. If this hypothesis holds true, TAAD can be regarded as a "network" disease, where a defect in a part of the network component leads to the disruption of the aortic wall integrity, making it susceptible to the acute or chronic destruction due to the hemodynamic and neurohumoral stress. It will also provide a unified view for familial monogenic TAAD and non-familial sporadic TAAD.

Currently, it is unknown why SmgGDS can regulate multiple aspects of TAAD. It may be that because SmgGDS is a multifunctional molecule regulating multiple small G proteins, it can be a central regulator of TAAD pathogenesis by directly interacting with multiple aspects of the TAAD network. Alternatively, SmgGDS may interact with only a part of the network, but SmgGDS can affect the network as a whole because TAAD network is always working in concert by unknown mechanism. In this sense, the paper by Nogi *et al.* provides more questions than answers to decipher the mystery of TAAD, a hallmark of the papers that cultivate a new research field. In either case, SmgGDS can be an entry point to test if TAAD is indeed a "network" disease, if unified view for familial and sporadic TAAD can be obtained, and eventually, diagnostic and therapeutic strategies can be built on the understanding of the TAAD pathogenesis.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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