



SmgGDS, a new piece in the thoracic aortic aneurysm and dissection puzzle

Marjolijn Renard

Center for Medical Genetics, Ghent University, Ghent, Belgium

Correspondence to: Marjolijn Renard, Center for Medical Genetics, Corneel Heymanslaan 10, B-9000 Ghent, Belgium.

Email: marjolijn.renard@ugent.be.

Provenance: This is an invited Editorial commissioned by the Section Editor Lei Zhang (Department of Vascular Surgery, Changhai Hospital, Second Military Medical University, Shanghai, China).

Comment on: Nogi M, Satoh K, Sunamura S, *et al.* SmgGDS Prevents Thoracic Aortic Aneurysm Formation and Rupture by Phenotypic Preservation of Aortic Smooth Muscle Cells. *Circulation* 2018. [Epub ahead of print].

Submitted Oct 01, 2018. Accepted for publication Oct 15, 2018.

doi: 10.21037/jtd.2018.10.68

View this article at: <http://dx.doi.org/10.21037/jtd.2018.10.68>

Considerable morbidity and mortality is associated with thoracic aortic aneurysm and dissection (TAAD). In addition to environmental factors, genetic defects can contribute to the development of TAAD. Our understanding of the pathogenesis of TAAD has evolved substantially in the last years.

Proper function and structural integrity of the thoracic aortic wall are ensured by correct sensing of the chemomechanical environment by cells in the aortic wall (e.g., vascular smooth muscle cells, VSMC) and regulation of the extracellular matrix and cytoskeleton in response (1). Studies have shown that this response is driven by Angiotensin-II (AngII) signaling (2). AngII signaling in turn regulates a plethora of signaling pathways, including TGF- β , RhoA and MAPK, which are involved in VSMC contraction and morphology (3). Extensive crosstalk exists across these pathways. Moreover, all these pathways have already been shown to be involved in TAAD one way or another (4). The importance of intact and correct functioning VSMC is indeed stressed by the discovery that pathogenic variants in genes involved in the VSMC contractile-elastic unit (*ACT2*, *MYH11*, *MYLK*, *PRKG1*) cause syndromic and non-syndromic forms of TAAD (5). In addition, pathogenic variants in other genes (extracellular matrix or TGF- β pathway) causing TAAD also affect VSMC function, either through disruption of ECM-cell contact, altered differentiation of VSMC (from a contractile phenotype to a secretory or pro-inflammatory phenotype), or VSMC

apoptosis (5). Aside from the direct effects on VSMC, the aortic wall of patients suffering heritable forms of TAAD is also characterized by aberrant TGF- β signaling, production of reactive oxygen species (ROS), and increased MMP activity (6). Importantly, AngII is a known key mediator of oxidative stress leading to the production of ROS (7). It also induces inflammation, affects endothelial function and VSMC growth, and regulates ECM formation (7).

The Smg GDP dissociator stimulator protein (SmgGDS) encoded by the *RAP1GDS1* gene stimulates GDP/GTP exchange of a group of small GTP-binding proteins, such as Rap and RhoA (8). Relatively little is known about the function of SmgGDS. Importantly, however, SmgGDS has previously been shown to be critical for myosin filament organization and consequently contraction of VSMC (9). In that study, the effect of SmgGDS on VSMC morphology and contraction was demonstrated to be mediated through RhoA signaling.

Here, Nogi and colleagues tested the hypothesis that SmgGDS is involved in the pathogenesis of thoracic aortic aneurysm and dissection (10). First, they demonstrated that SmgGDS is more weakly expressed in the ascending aorta and VSMC of TAAD patients compared to controls. In addition, *FBNI*, *ACTA2* and *MYH11* expression was also significantly lower in VSMC of TAAD patients compared to controls. Following this finding, the authors tested this hypothesis further in an *Apoe*^{-/-}SmgGDS^{+/-} mouse model infused with AngII. Four weeks of AngII infusion

resulted in thickening of the aortic media, degradation of the ascending aorta wall and development of thoracic aortic aneurysms in these mice compared to control mice. AngII-infusion of ApoE^{-/-}SmgGDS^{+/-} mice also triggered thoracic aortic dissection. Furthermore, a third of the AngII-ApoE^{-/-}SmgGDS^{+/-} mice died prematurely due to aortic rupture of the thoracic aorta. Hence, the authors postulate that SmgGDS plays a protective role against development of thoracic aortic aneurysm and dissection. A pathogenic mechanism that is put forward by the authors is that deletion of SmgGDS affects the differentiation of VSMC into their contractile phenotypic status, instead VSMC switch to a synthetic or inflammatory phenotype. This results in a diminished capacity of the cells to respond to cyclic stretch. Evidence is provided by decreased expression of several genes involved in VSMC contraction, as well as reduced fibrillin-1 expression. The adverse effect of SmgGDS on VSMC phenotype is mediated through the RhoA pathway. Surely, RhoA, Rap1, and RhoC activity is also reduced in murine VSMC from AngII-ApoE^{-/-}SmgGDS^{+/-} mice *in vitro* in response to cyclic stretch compared to controls. Furthermore, SmgGDS deficiency also affects TGF- β signaling, as is implied by lower levels of TGF- β 1 and pSMAD2/3 in AngII-ApoE^{-/-}SmgGDS^{+/-} mice compared to control mice. Reported features of aortic disease are inflammatory infiltration of the wall, oxidative stress, and increased MMP activity in the extracellular matrix (11-15). In accordance, increased migration of inflammatory CD45⁺ cells was noted in the adventitia of AngII-ApoE^{-/-}SmgGDS^{+/-} mice compared to control mice. Also, AngII-ApoE^{-/-}SmgGDS^{+/-} mice show increased *Nox1* and *Rac1*, elevated NADPH oxidase activity, increased ROS production, and reduced *Nrf2* levels compared to control mice. These are all signs that SmgGDS is required for protection against oxidative stress in VSMC. A mechanistic link between SmgGDS-mediated Rac1 degradation, NADPH oxidase activities and ROS production has been suggested previously and is thus confirmed here (16,17). Furthermore, AngII-ApoE^{-/-}SmgGDS^{+/-} mice, as well as VSMC from human TAAD patients, are characterized by cyclophilin A (CyPA)-mediated MMP-2 and -9 activation and increased ROS production. Hence, these typical changes in the diseased aortic wall are the result of pathological phenotypic changes in VSMC driven by SmgGDS deficiency.

A major finding in this study is the complete rescue of the described phenotype achieved by local overexpression of SmgGDS in the ascending aortic wall

of AngII-ApoE^{-/-}SmgGDS^{+/-} mice. This finding opens therapeutic perspectives if drugs can be identified that stimulate SmgGDS production. Currently, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) have been shown to upregulate SmgGDS selectively in aortic endothelial cells (18). Despite the cell-specific action of the investigated statins, they are able to reverse AngII-induced medial thickening and perivascular fibrosis of coronary arteries in wild-type mice (16). This was, however, not the case in SmgGDS^{+/-} mice (16). In addition, a clinical study by Angeloni and colleagues reported that statins could reduce the growth rate of ascending aortic aneurysms (19). The underlying mechanism involved anti-inflammatory actions and reduction of oxidative stress, but the details are not clear yet. Evidently, it is important to further explore this possible therapeutic avenue, especially since to date there is no therapeutic agent that is able to stop the growth of aneurysms and the occurrence dissections. For now, the best approach is to slow down the rate of aortic growth. Current standard of therapeutic care are beta-blockers or angiotensin receptor blockers (ARBs), when beta-blockers are not tolerated, although neither of these drugs impact outcome in a meaningful way (20).

Naturally, novel discoveries come with new questions. To date, the precise pathogenic mechanism driving SmgGDS-mediated VSMC phenotypic switching and the consequences thereof is not clear and needs further study. Another question that remains unanswered in the study of Nogi and colleagues is whether, besides pathological VSMC phenotypic switching, VSMC are also more prone to apoptosis. AngII-infusion of an Acta2^{-/-} mouse model, for example, induced TAAD with marked increase in oxidative stress and matrix metalloproteinase activity, and this due to both VSMC dysfunction and apoptosis (21).

Furthermore, the authors chose to use a chemically induced TAAD mouse model instead of a genetic mouse model to cross with the SmgGDS^{+/-} mice. The question is whether the SmgGDS-mediated effect described in the manuscript of Nogi and colleagues is also relevant in heritable forms of TAAD. Of note, the AngII-infused ApoE^{-/-} mouse model is a popular mouse model for pre-clinical aneurysm research, however, a study by Trachet et al. shows that this model is an aortic dissection model rather than an aneurysm model (22). Remarkably, however, no lethal dissection or rupture of the thoracic aortic occurred in AngII-ApoE^{-/-} mice during this study.

Identifying SmgGDS as a possible mediator of the VSMC-driven pathogenic mechanism in TAAD also

encourages considering the potential use of SmgGDS as biomarker as implied by the authors. Biomarkers that could predict which patients are at risk for developing aortic aneurysms and dissections are direly needed. At present, the aortic diameter is used as the sole indicator for identifying patients at risk for aortic dissection. This is, however, an unreliable indicator. Several biomarkers have been proposed, an example of which is the promising fibrillin-1 fragments (23). Nonetheless, firm evidence for the prognostic value of these biomarkers is still lacking.

To date, no TAAD patients have been identified with pathogenic variants in the *SmgGDS* gene. In agreement with the authors, it would be interesting to screen the gene in TAAD patients.

The study of Nogi and colleagues adds yet another piece to the TAAD puzzle. Untangling the additional questions raised by this study may advance clinical care of TAAD patients.

Acknowledgements

The author is a postdoctoral fellow supported by the Research Foundation - Flanders.

Footnote

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

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Cite this article as: Renard M. SmgGDS, a new piece in the thoracic aortic aneurysm and dissection puzzle. *J Thorac Dis* 2018;10(Suppl 33):S4133-S4136. doi: 10.21037/jtd.2018.10.68