Four-and-a-half LIM-domain 2 secretion is increased in the dilated aorta of bicuspid aortic valve patients

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Background
A bicuspid aortic valve (BAV) is the most common congenital heart defect and consists of a two leaflet aortic valve instead of the regular three leaflet valve. A BAV is accompanied by a thoracic aortic aneurysm (TAA) in 50% of the adult patients. TAA is characterized by loss of contractile smooth muscle cells (SMCs) and fragmentation of the elastic lamellae. Aside from surgical removal of the ascending aorta, there is no treatment option currently available. A protein that is involved in the SMC phenotype is Four-and-a-Half LIM-domain 2 (FHL2), a scaffold protein that interacts with many genes shown to be involved in TAA development and can affect gene transcription.

Purpose
To investigate the role of FHL2 in BAV associated TAA.

Methods and Results
The aortic wall of BAV patients with and without aortic dilation was stained for FHL2 expression, in which we observed an increase in FHL2 expression in the tunica media of the dilated compared to the non-dilated aorta of BAV patients. Moreover, FHL2 was present in a speckled pattern, which showed no overlap with alpha-smooth muscle actin staining. This speckled pattern led to the hypothesis that FHL2 is secreted within the vessel wall. Western blot analysis was used to study if FHL2 is secreted by SMCs and/or endothelial cells (ECs), and confirmed that FHL2 is indeed present in conditioned medium of these cells and is secreted in exosomes. A luciferase reporter assay showed that overexpression of FHL2 in SMCs decreased Cyclin D1 promotor activity. Interestingly, when conditioned medium from SMCs overexpressing FHL2 was added to WT SMCs, Cyclin D1 promotor activity decreased as well. Finally, we determined if the presence of FHL2 in plasma of BAV patients could serve as a biomarker for aortic dilation, but so far no significant correlation between FHL2 levels in plasma and aortic dilation could be distinguished. We are currently increasing the number of patients analyzed.

Conclusions
In BAV patients with aortic dilation, the tunica media shows an increase of FHL2. We found that FHL2 is present in exosomes and can regulate SMC proliferation. Therefore, FHL2 might play a role in SMC phenotypic switch in aortic aneurysm formation.