Background: Congenital heart defects (CHD) are the most common birth defects, often presenting with abnormal heart valves. How mechanical and genetic signals interact to drive proper heart valve development is not understood. Our preliminary results identify endocardial (EC) primary cilia as a necessary link between mechanical forces and the transcription of genes responsible for heart valve formation, acting in a Ca\textsuperscript{2+} and cytoskeletal-dependent manner to promote endothelial to mesenchymal transition (EndoMT) in heart valve progenitors (cushions).

Methods: To see how EC primary cilia and expression of Klf2 and 4, transcription factors upstream of EndoMT (Klf2 promotes EndoMT, Klf4 inhibits it), change spatially over heart cushion development, we are utilizing in situ hybridization and immunofluorescence in mice, and various transgenic lines marking endocardium, cilia, and the promoter regions of Klf2/4 in live zebrafish. To test whether Klf2/4 depend on cilia, ciliary Ca\textsuperscript{2+} and/or mechanical forces, we are using various mutant models, such as Ift20 and Kif3a (cilia KOs), Ncx/Tnnt2a (heartbeat KO, mouse and zebrafish, respectively), and Pkd2 (ciliary Ca\textsuperscript{2+} KO).

Results: I have found that Klf2 and 4 get induced in ciliated ECs as the heart becomes contractile. These ciliated ECs lose their cilia (deciliation) in distinct regions of the heart, such as the atrioventricular canal (AVC), in response to increasing wall shear stress (WSS). This leads to loss of Klf4, but not Klf2, allowing EndoMT to occur and cushion formation to progress. Altered Klf4 expression in mouse embryos with mutations affecting cilia biogenesis, ciliary Ca\textsuperscript{2+} signaling and cardiac contraction suggests that Klf4 downregulation is dependent on loss of ciliary Ca\textsuperscript{2+} signaling, and Klf4 upregulation is cilia-independent when WSS is high and strong enough to cause cytoskeletal-dependent Klf4 transcription. This implicates both ciliary Ca\textsuperscript{2+} signaling and the mechanical presence of cilia acting as a lever on the cytoskeleton as mechanisms of translating WSS into Klf4 regulation.

Conclusions: Our data provides insight into the mechanism controlling Klf2/4 mechanosensitivity during heart cushion formation, and highlight a role for cilia as mechanosensors during cardiogenesis.

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(data provided below)