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Control of Cardiac Jelly Dynamics by Notch1 and Nrg1 Defines the Building Plan for Cardiac Trabeculation.

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Abstract:

In vertebrate hearts, ventricular trabecular myocardium develops as a sponge-like network of cardiomyocytes critical for efficient cardiac contraction in the early embryo, and for ventricular conduction, septation, and wall thickening through the process of compaction in the foetal heart. Defective trabeculation at early developmental stages leads to embryonic lethality whereas defects at later stages can lead to Non-Compaction Cardiomyopathy, the third most commonly diagnosed cardiomyopathy in adults.

There are divergent views on when and how trabeculation is initiated in different species. In mice, the onset of trabeculation has not been formally addressed, but is proposed to begin at embryonic day (E)9.0 as cardiomyocytes form radially-oriented ribs. Endocardium-myocardium communication is essential for trabeculation, with numerous signalling pathways identified, including Neuregulin1 (Nrg1) and Notch1. Late disruption of the Notch1 pathway causes Non-Compaction Cardiomyopathy. Although mutants in cardiac jelly extracellular matrix (ECM) genes Has2 and Vcan lack trabeculae, and matrix metalloprotease ADAMTS1 activity at E14.5 promotes total cardiac jelly degradation and trabecular growth arrest, the role of ECM dynamics and its molecular regulation during early trabeculation is poorly understood.

Here we present a new model of cardiac trabeculation starting as early as the heart tube forms (E8.0), integrating for the first time dynamic endocardial and myocardial cell behaviours, and ECM remodelling, and revealing new epistatic relationships for known signalling pathways. Notch1 signalling promotes ECM degradation during formation of endocardial projections critical for individualization of trabecular units, while Nrg1 promotes myocardial ECM synthesis, necessary for trabecular rearrangement and growth. These systems interconnect through Nrg1 control of Vegfa, yet act antagonistically to establish trabecular architecture. Furthermore, these insights allowed the prediction of persistent cardiac jelly and trabecular growth as a potential cause of disease in a murine Non-Compaction Cardiomyopathy model, providing new understanding of congenital heart disease pathophysiology.

References:

Del Monte-Nieto G, Ramialison M, Adam AAS, Wu B, Aharonov A, D'Uva G, Bourke LM, Pitulescu ME, Chen H, de la Pompa JL, Shou W, Adams RH, Harten SK, Tzahor E, Zhou B, Harvey RP. Control of cardiac jelly dynamics by NOTCH1 and NRG1 defines the building plan for trabeculation. **Nature**. 2018 May;557(7705):439-445. doi: 10.1038/s41586-018-0110-6. Epub 2018 May 9. PMID: 29743679.