"Proof of genetic heterogeneity in cardiac septal defects and in heterotaxy"

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Abstract
The prevalence of congenital heart defects is approximately 1% of all births, yet the causative factors remain largely uncharacterized. For the majority, the physiopathogenesis is believed to be multifactorial, hindering the identification of causative factors. However, several genes have been identified for septation defects that are part of a syndrome. Yet, in non-syndromic septal defects it has been difficult to identify predisposing genetic factors. When I started this thesis project, only one gene had been identified to be responsible for non-syndromic septal defects. We collected families in which two or more individuals were affected with non-syndromic cardiac septal defects. In five families, arrhythmia was associated with ASD/VSD. We screened the CSX/NKX2-5 gene, previously identified to be responsible for ASD and PR prolongation, and identified 3 novel missense mutations. In parallel, we screened the CSX/NKX2-5 gene in sporadic and familial cases of other cardiopathies, but...

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In this model, the development of the cardiac valve occurs in 4 steps. First, Notch and Wnt/β-catenin signaling create a subset of endothelial cells competent to undergo EMT, controlling the production of growth factors and structural elements required for the initiation of EMT. After specification, cells fated to transdifferentiate must delaminate and activate a mesenchymal program. TGFβ signaling through Snail/Slug results in decreased VE-cadherin expression, allowing endocardial cells to separate. Concomitant with the delamination process, endocardial cells must repopulate to replace the cells that will undergo EMT. VEGF signaling through NFATc1 increases endothelial cell proliferation perhaps contributing to repopulation. Cells that delaminate begin the process of transdifferentiation and migration to the cardiac jelly. TGFβ synergizes with BMP to promote EMT. Hyaluronic acid signaling may also mediate the migratory process into the cardiac jelly. Conversely, EGFR signaling may limit the extent of EMT. Finally the process of creation a cardiac cushion must ensure that the localized cushion swellings can remodel into thin fibrous sheets. Evidence suggests that neurofibromin acts through inhibition of Ras signaling to limit the extent of EMT.