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Zebrafish Models of Cardiac Valve Development and Disease

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SUMMARY

Cardiac valves derive from endocardial cells and function throughout the life of vertebrates to prevent retrograde blood flow. We have identified a number of mutants in different stages of valve development and work on characterizing and cloning the corresponding genes. These mutations disrupt atrioventricular (AV) valve development at discrete stages, indicating that such a complex morphogenetic process can be broken down into genetically separable steps.

We have identified a mutation in the glycyl t-RNA synthetase (GARS) where valve development comes to a halt, at a stage following atrioventricular canal specification and squamous to cuboidal epithelium transition. We have also identified two novel alleles of weak atrium that carry premature stop codons in myh6 and develop pericardial edema and AV valve stenosis by 60 hpf. However, when the pericardial edema is surgically released, adult animals can be raised indicating that the sole beating of the ventricle in the zebrafish heart can support circulation throughout development and adulthood. Nevertheless, the changes in atrial contractility and hemodynamics interfere with the wild-type remodelling/matu-ration of the AV valves (from two to four cusps) and result in a hypertrophic ventricle. The 3rd line we isolated has an outflow tract stenosis by 72hpf and the bi-directional blood flow causes dilation of the heart chambers and single-layer endocardial cells at the AV canal. Finally, we also isolated an adult viable mutant line where the heart does not loop properly resulting in delayed AV valve development.

The long-term aim of our efforts is to find out how heart valves form and function throughout the life of vertebrates.