Effects of *Pax3* mutation and Neural Crest genetic ablation on congenital heart function and embryonic lethality

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Abstract

Congenital heart defects (CHDs) occur in approximately one percent of births every year (American Heart Association, 2008). This makes it the most frequently occurring congenital defect in humans. My research is aimed at using two mutant cardiac neural crest (CNC) mouse models to study the mechanisms underlying congenital heart failure *in utero* with particular interests in understanding the processes of outflow tract (OFT) septation and myocardial homeostasis. The first mouse model is a *Pax3* systemic knockout, which is lethal by mouse gestational day14, and has an insufficient number of migratory CNC cells. The second mouse model is a *Wnt1Cre*-mediated neural crest-ablated model, which is surprisingly viable and survives to birth, despite having no migratory CNC cells.

My data indicates that both mouse models have similar heart structural anomalies including failure of the OFT to divide and interventricular septation defects. However, *in utero* heart function is significantly perturbed in *Pax3* mutants when compared to that of the ablated mutant model. Via comparison of these two mutant mouse models, I have been able to assess the tissue-specific contribution of the CNC cell lineage during *in utero* heart morphogenesis, as well as to identify the beta-adrenergic pathway as the underlying mechanistic pathway that is important for the observed differences in myocardial function and subsequent congenital heart failure and lethality in the *Pax3* mutants. By doing so, I am now able to demonstrate pharmacological rescue of the *Pax3* mutants to birth, via bypassing or stimulation of the aforementioned pathway.

By understanding the causes of congenital heart failure and subsequent lethality in the *Pax3* genetic model, and successfully achieving pharmacological rescue to birth, I believe the results of my project will allow me to translate my findings into better treatment strategies for newborn patients with similar CHDs.

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