STRONG CHILDREN'S RESEARCH CENTER

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ABSTRACT

Title: **Role of CyPD in the developing mouse heart**

Neonatal heart failure is a persistent problem occurring with an incidence of 12,000–35,000 children per year in the United States. Therefore, it is imperative that we study the development of the heart and the possible role of the unclear mechanisms that occur during activation of the electron transport chain (ETC). Complex V (ATP synthase) binds a chaperone protein known as cyclophilin D (CyPD) that is known to regulate the mPTP, which has a role in myocyte differentiation and mitochondrial maturation. Previous data shows that closing the mPTP by inhibiting CyPD with cyclosporin A (CsA) and NIM811, increases maturation of myocytes *in vitro* and significantly increased cardiac function in neonatal mouse hearts *in vivo*.[4] The aim of this study is to determine the effect of CyPD -/- and the CyPD inhibitors cyclosporin A (CsA) and NIM811 in mitochondrial biology, gene expression and bioenergetics over the development of the heart. This project tested the hypothesis that CyPD Inhibition and CyPD -/- inducing mPTP closure will increase mitochondrial function and promote cardiomyocyte maturation during heart development. To explore this possibility, we observed WT and CyPD -/- mice at different times in embryonic and postnatal development. Results show that during cardiac development, the Electron Transport Chain proteins and activity increase over the development of the heart. There are higher levels of MtCO1 and ATP5A protein at weaning and adult hearts of CYPD -/- mice. Moreover, CyPD deletion decreases citrate synthase (CS) activity throughout gestation increasing ETC efficiency. Also, mRNA levels show a dramatic increase in ETC genes in the hearts of weanlings and adult mice. Interestingly, Ratios MYH6/MYH7 are higher in CYPD -/- suggesting an increase in cardiomyocyte cytoskeletal maturity. In relation, hypoxia increases cardiomyocyte proliferation by reducing mitochondrial activity while NIM and CSA increase mitochondrial activity and promote differentiation. This data supports the idea that CyPD -/- and the CyPD inhibition in the development of the heart and could be a potential approach for therapeutic manipulation to increase the cardiac function on pre-term kids.

References:

1.Hsu DT, Pearson GD. Heart failure in children: part I: history, etiology, and pathophysiology. Circ Heart Fail 2009; 2:63–70.
2. Hom JR, Quintanilla RA, Hoffman DL, de Mesy Bentley KL, Molkentin JD, Sheu SS, Porter GA Jr. The permeability transition pore controls cardiac mitochondrial maturation and myocyte differentiation. Dev Cell. 2011 Sep 13;21(3):469-78. doi: 10.1016/j.devcel.2011.08.008. Erratum in: Dev Cell. 2011 Nov 15;21(5):975. PMID: 21920313; PMCID: PMC3175092.
3. Beutner, G.; Alanzalon, R. ; Porter, G. Cyclophilin D regulates the dynamic assembly of mitochondrial ATP synthase into synthasome. Nature Scientific Reports. 2017, Vol 7, Article 14488, 1-12.
4. Baines and Molkentin, 2009; Brookes et al., 2004; Crompton, 1999; Gunter and Sheu, 2009; Halestrap, 2009; Lemasters et al., 2009
5. Lingan JV, Alanzalon RE, Porter GA Jr. Preventing permeability transition pore opening increases mitochondrial maturation, myocyte differentiation and cardiac function in the neonatal mouse heart. Pediatr Res. 2017 Jun;81(6):932-941. doi: 10.1038/pr.2017.19. Epub 2017 Jan 31. PMID: 28141792.