STRONG CHILDREN'S RESEARCH CENTER

Summer 2017 Research Scholar

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ABSTRACT

Title: Role of Modified Cyclophilin D Activity in Cardiac Mitochondrial Supercomplex Formation

Background: The mitochondrial permeability transition pore (PTP) is thought to be derived from ATP Synthase (complex V) of the ETC. Recent research studies suggest that CyPD regulates the assembly of complex V into supercomplexes called synthasomes, and thus potentially controls the PTP formation. In addition, preliminary data from the Porter lab indicate that ETC activity and synthasome formation, which enhances ATP production efficiency, increases during the final stage of myocyte differentiation in the neonate. We hypothesize that if CyPD is active, then it prevents synthasome formation and will increase the probability that complex V monomers would form the PTP.

Objective: Determine the effects of modified CyPD activity on supercomplex formation and the location of CypD within these supercomplexes using wildtype(WT) and mutant forms of CyPD.

Results: Transfection of $CyPD^{-/-}$ cells using 800ng of CyPD modified RNA was successful as demonstrated by probing for CyPD in Western Blots and cellular imaging. Data suggest that inhibition and deletion of CyPD increase synthasome formation, while acetylation at K166Q may decrease formation. In addition, treatment of WT cell cultures with CsA and NIM811 shifts CyPD from supercomplexes to a lower molecular weight complex of unknown composition. Lastly, $CyPD^{-/-}$ cells transfected with WT RNA appear to have CyPD bound to synthasomes.

Conclusion: Acetylation of CyPD may play a role of synthasome formation and PTP opening.

References:

1. Alavian KN, et al. "An uncoupling channel within the c-subunit ring of the F1FO ATP synthase is the mitochondrial permeability transition pore." *Proc Natl Acad Sci U S A*. 2014;111(29).
2. Beutner, et al. "Cyclophilin D regulates the dynamic assembly of mitochondrial ATP synthase into synthasomes." *Submitted for publishing*. 2017.