Title: Mechanisms of Adenosine-Mediated Fetal Programing of Disease.

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Research Project Description:

We discovered that *in utero* alteration in adenosine action (caffeine exposure) leads to adverse effects in embryonic and adult murine hearts. We observe that *in utero* caffeine exposure leads to abnormal cardiac function and morphology in adults, including impaired response to β-adrenergic stimulation. Importantly, we find that inhibition of adenosine action during cardiac development leads to a phenotype in adulthood similar to dilated cardiomyopathy (DCM) and is associated with altered DNA methylation patterns.

Using siRNAs to knockdown expression of each of the DNA methyltransferases (DNMTs) in embryonic cardiomyocytes, we identified DNMT3a as a unique regulator of cardiomyocyte contractility, cellular morphology, and gene expression. Based on these data, **we hypothesize that *in utero* alteration in DNMT activity and/or expression leads to altered DNA methylation and gene expression patterns in adult hearts. In addition, we postulate that these changes in gene expression lead to an increased risk of developing heart failure in adulthood. We also postulate that altered adenosine action can trigger this cascade of events.**

Some of the potential roles of medical students in this project would include 1) isolation, culturing and treating embryonic cardiomyocytes with siRNA to knockdown DNMT expression followed by analysis of contractility, gene expression and DNA methylation patterns. 2) Analysis of adult and juvenile transgenic mice that have had DNMT3a knockouted out globally or only from cardiomyocytes. This analysis would include echocardiography, electrocardiography, and blood pressure analysis.

1. Buscariollo D.L., Fang X., Greenwood V., Xue H., Rivkees, S.A., and Wendler C.C. (2014) Embryonic caffeine exposure acts via A1 adenosine receptors to alter adult cardiac function and DNA methylation. *PLoS ONE* 9(1): e87547. PMID 24475304.

2. Fang X., Mei W., Barbazuk W.B., Rivkees S.A., and Wendler C.C. (2014) Caffeine Exposure Alters Cardiac Gene Expression in Embryonic Cardiomyocytes. *American Journal of Physiology Regulatory, Integrative, and Comparative Physiology.* Oct 29:ajpregu.00307.2014. doi: 10.1152/ajpregu.00307.2014.

3. Wendler, C.C., Busovsky-McNeal, M., Ghatpande, S., Kalinowski, A., Russell, K.S., and Rivkees, S.A. (2009) Embryonic Caffeine Exposure Induces Adverse Effects in Adulthood. *The FASEB Journal* 23:4, 1272-1278. PMCID: PMC2660649

4. Buscariollo D.L., Breuer G.A., Wendler C.C., Rivkees S.A. (2011) Caffeine Acts via A1 Adenosine Receptors to Disrupt Embryonic Cardiac Function. PLoS ONE 6(12): e28296.