GLOBAL CHANGES IN THE CELLULAR EPIGENETIC MACHINERY WITH DEVELOPMENT OF LEFT VENTRICULAR HYPERTROPHY

ACC Moderated Poster Contributions
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Background: The molecular basis underlying activation of the fetal gene program during development of left ventricular hypertrophy (LVH) is poorly understood. Epigenetics is the study of non-genetic code modifications that alter gene expression. No studies have assessed global epigenetic changes in LVH. We studied DNA methylation and epigenetic modifying gene expression profiles between spontaneously hypertensive rats (SHR) and age-matched controls (WKY) to test the hypothesis that there are global epigenetic changes with LVH.

Methods: SHR and WKY rats (n=4) were euthanized at 2 and 10 months of age after blood pressure (BP) measurement and echocardiography were performed. Nucleic acids were extracted from LV tissue. Global DNA methylation levels were assessed by HPLC/mass spectroscopy at each time point. RNA expression profiling was performed for 168 epigenetic modifying genes using RT2 Profiler RT-PCR kits (SA Biosciences; n=3) at 2 and 10 months of age.

Results: SHRs had higher BP at 2 months and developed LVH by 10 months compared to WKY (p<0.05). Global DNA methylation was not significantly different between 2-month old WKY and SHR (1.69±0.02% vs. 1.78±0.06%, p=0.055) but was significantly higher in SHR at 10 months (1.93±0.06% vs. 2.06±0.04%, p=0.03). At 2 months, epigenetic modifying gene expression profiles were similar between WKY and SHR (6 genes ≥1.5 fold change, p<0.05). Profiles were also similar between 2- and 10-month WKYs (5 genes ≥1.5 fold change, p<0.05). There was global downregulation of epigenetic modifying gene expression in 10-month compared to 2-month SHRs (47 genes ≥1.5 fold change, p<0.05) as well as in 10-month WKYs compared to 10-month SHRs (19 genes ≥1.5 fold change, p<0.05). Epigenetic modifying genes were mostly downregulated in SHRs with a minority of genes overexpressed compared to controls. No predominance of any particular gene class was found.

Conclusions: These new data suggest that DNA methylation is increased concomitantly with altered expression of epigenetic modifiers during the development of LVH. Modification of the cellular epigenetic machinery is a previously unexplored area of cardiac biology and a potential target for therapeutic intervention.