SEX DIFFERENCES IN CARDIAC STRUCTURE AND FUNCTION OF ZUCKER DIABETIC FATTY MALE AND FEMALE RATS

Kelly J. Lum-Naihe

Lakshmi Pulakat, PhD, Thesis Supervisor

ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death for American adults, and diabetes mellitus (DM) is an independent risk factor for CVD. Diabetic women have a greater risk for CVD compared to age-matched diabetic men, though underlying mechanisms remain unclear. We have observed that young, male and female Zucker diabetic fatty (ZDF-M and ZDF-F) rats display hyperglycemia and mild diastolic dysfunction. However, only ZDF-F showed regions of gross cardiac damage. In an effort to understand why diabetic females have a greater risk for CVD, we examined differences in cardiac gene expression of two families of microRNAs (miR-29 and miR-208) and genes they target by qRT-PCR. We hypothesized that sex differences exist in the expression of both miRNA families which may contribute disease progression and increased risk of myocardial damage in diabetic females. Notably, we observed a sex bias in healthy rats: ZL-F had greater Agtr2, Med13 and miR-208 expression, while ZL-M had increased cardiac Gata4, Gdf11, Nppb and miR-29b. In both ZDF-F and ZDF-M, the miR-29 family of miRNAs were upregulated whereas only ZDF-F showed a suppression in Agtr2. We additionally show that in vitro, transfection of primary human coronary artery smooth muscle cells (hCAVSMCs) with miR-29b increases the number of TUNEL- and PI-positive cells, but a 4 day exposure to 25mM glucose failed to induce an upregulation of miR-29, suggesting short-term hyperglycemia does not upregulate miR-29 expression in hCAVSMCs. We conclude that sex differences in Agtr2 and miR-29b expression may underlie higher risk for CVD in young ZDF-F.