Persistent disrupted mitochondrial adaptation in primary vascular cells from a diabetic model

Abstract:
People with diabetes (DM) have an excess burden of cardiovascular disease (CVD). Impairments in vascular contractility predict poor CVD outcomes, and mitochondria are essential for arterial contraction and relaxation. Mitochondrial dysfunction is observed with DM and insulin resistance. Our laboratory has reported failed vascular mitochondrial adaptation to exercise in DM rats. We hypothesize that repairing vascular mitochondrial function could restore contractility in DM. We employed primary aortic smooth muscle cells (SMC) from a lean, insulin resistant DM rat, Goto-Kakizaki (GK), and the Wistar (W) control to test mitochondrial adaptation to metabolic stress. SMC were exposed to low glucose (LG, 5 mM) or high glucose (HG, 25 mM) treatments for 1, 4 and 24 hours. Mitochondrial respiration, superoxide and dynamics (fission and fusion) were measured. Respiration in W SMC exposed to HG was unchanged compared to the LG control, but was decreased after 4 hours of HG treatment in the GK SMC (p≤0.05). GK SMC have significantly increased whole cell production of H2O2 as compared to W SMC, but not mitochondrial superoxide after 4 hours of HG treatment. In contrast, W SMC exposed to HG significantly had increased superoxide relative to LG control (p<0.05). No differences in total mitochondrial complex expression were seen in baseline W and GK SMC comparisons; phosphorylated eNOS and PGC-1α, direct upstream regulators of mitochondrial biogenesis, were increased and decreased, respectively, in the GK SMC as compared to the W SMC (p<0.05). Preliminary quantitative immunohistochemistry shows a significant mitochondrial biogenesis and fusion response to HG treatment in the W SMC; conversely, GK SMC showed a decrease in mitochondria after 4 hours of HG treatment. Fis 1 was significantly decreased at 1 hour in W and increased at 24 hours in the GK (p<0.05). Significant changes in fusion included decreased OPA1 and mfn1 in W SMC and increased OPA1 and decreased mfn1 in the GK. Overall, these data reveal that distinct mitochondrial adaptation to a hyperglycemic state is persistent in DM cells ex vivo. Primary SMC can be used as a model to define signaling events determining these changes and development of therapeutic targets to repair contractility.

Research Category: Basic Science