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CHS Grant-in-Aid:

“CARD9 Regulates Obesity-Induced Cardiac Mitochondrial Dysfunction”

Obesity has causative effects on metabolic syndrome and heart dysfunction. Related adverse myocardial remodeling and heart failure are devastating causes of morbidity and mortality in the United States. The overall goal of the present proposal is to determine how obesity, induced by a Western diet (WD), causes cardiac mitochondrial dysfunction.

Obesity or diet-induced nutrient stress is associated with low grade inflammation and macrophage accumulation in adipose tissue. Caspase recruitment domain-containing protein (CARD9) plays a central role in the innate and adaptive inflammatory responses. CARD9 mediates p38 mitogen-activated protein kinase (MAPK) in macrophages and p38 MAPK has been involved in the regulation of peroxisome proliferator activator receptor $\gamma$ coactivator-1$\alpha$ (PGC1$\alpha$) in skeletal muscle. Using immunoblotting and real-time PCR, we have observed that PGC1$\alpha$, nuclear respiratory factor-1 (NRF-1), and transcriptional factor of activated mitochondria (Tfam) were down-regulated in the heart of WD-induced obese (WDIO) mice. Therefore, we hypothesize that: WDIO induces cardiac mitochondrial dysfunction via CARD9/p38 MAPK-mediated phosphorylation of PGC1$\alpha$ and down-regulation of NRF-1/Tfam signaling. To test this hypothesis, we will employ a novel transgenic CARD9$^{-/-}$ mouse model to dissect the signaling pathways responsible for cardiac mitochondrial dysfunction in obese mice. Additionally, we will utilize echocardiography to assess cardiac dysfunction. We believe that understanding the effect of CARD9 on cardiac mitochondrial dysfunction in WDIO mice is critical for potential therapeutic interventions to cure heart diseases.