

Inhibition of the Mitochondrial Calcium Uniporter Reduces Oxidative Phosphorylation in SGK1-Knockout VSMC Upon Diet-Induced Obesity

Bao Tran¹, Wei Zhong³ and Sharon C. Francis, PhD^{2,3}

Obesity is linked to vascular diseases such as atherosclerosis and coronary artery disease which is a major underlying cause of heart attacks. While the mechanism is not fully known, altering mitochondrial respiration which occurs through oxidative phosphorylation (OXPHOS) may influence the development of vascular disease during obesity. Our previous data with diet-induced obese (DIO) mice demonstrated that serum and glucocorticoid-inducible kinase 1 (SGK1), which regulates cell metabolism, was up-regulated in vascular smooth muscle cells (VSMC) from the aorta. Knocking out SGK1 in VSMCs (KO^{SGK1}) was associated with higher OXPHOS and lower vascular disease relative to wildtype VSMCs (WT^{SGK1}) during DIO. The mitochondrial calcium uniporter (MCU) permits calcium uptake into the mitochondrial matrix causing stimulation of OXPHOS thereby contributing to maintenance of cellular energy homeostasis. We hypothesized that OXPHOS stimulation in KO^{SGK1} VSMC may be due to enhanced activity of the MCU. To test this hypothesis, an extracellular oxygen consumption (EOC) assay which measures OXPHOS was used to examine the role of MCU-mediated mitochondrial Ca²⁺ uptake on basal and maximal OXPHOS activity in WT^{SGK1} and KO^{SGK1} VSMCs. Thus, WT^{SGK1} and KO^{SGK1} VSMCs from DIO mice were treated ± Ru360 (10µM), a MCU inhibitor and ± FCCP (2.5µM) to stimulate maximal OXPHOS. Consistent with previous data, KO^{SGK1} VSMCs had significantly higher basal and maximal EOC compared to WT^{SGK1} VSMCs. Remarkably, RU360 significantly decreased both basal and maximal EOC in KO^{SGK1} VSMCs. Conversely, there was no effect of RU360 on EOC in WT^{SGK1} VSMCs. These results suggest a disparity in MCU activity in KO^{SGK1} VSMCs. In conclusion, these findings implicate mitochondrial Ca²⁺ uptake in stimulation of OXPHOS in KO^{SGK1} VSMCs.