Alterations in pyroptotic signaling mediated by phosphorylation of GRK2 and mitochondria functional alterations

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G protein-coupled receptors (GPCRs) mediate signal transduction from the extracellular environment to the intracellular space. Receptor signaling is terminated via receptor phosphorylation mediated by GPCR-kinases (GRKs). GRK2 is one of the main isoforms in the heart and is upregulated in heart failure (HF) patients. Recently, we and others have reported a non-canonical GRK2 signaling cascade that is initiated by ERK phosphorylation of GRK2 and subsequent mitochondrial translocation of this kinase. Notably, we found that phosphorylated GRK2 at S670 post-ischemia/reperfusion decreases mitochondrial glucose oxidation and pyruvate dehydrogenase (PDH) activity. A possible link was established between GRK2 and PDH using 2D-SDS PAGE combined with phospho-proteomics. Using a novel PDHα KI CRISPR Cas HEK cell line, we tested the hypothesis that this phosphorylation event regulates PDH activity. Utilizing cytosolic and mitochondrially-targeted pyruvate indicators we measured pyruvate levels in WT and KI HEK cells. Moreover, using a mouse model where GRK2 cannot translocate to the mitochondria (GRK2-S670A), in the presence or absence of myocardial infarction, we are investigating the role of GRK2 mitochondrial translocation, metabolic alterations, and gasdermin signaling. Further experiments will elucidate the precise role of mitoGRK2 on cardiac metabolism, PDH activity, and mechanisms of cell survival a priori and a posteriori to cardiac ischemic events relevant to understanding cardiac metabolic remodeling in disease progression.