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Mitochondrial CaMKII as a Novel Regulator of Cardiometabolic Dysfunction

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Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is an established negative regulator of cardiac injury. Both the expression and activity levels of CaMKII are elevated in models of heart failure such as ischemia-reperfusion (I/R) injury and myocardial infarction (MI). This is due in part to CaMKII's role in the regulation of excitation-contraction coupling, apoptosis, activation of hypertrophic programming, arrhythmias and pro-inflammatory signaling. We have recently identified a novel mitochondrial localization for CaMKII (mtCaMKII); importantly, there is an observed increase in mtCaMKII activation with left ventricular dilation following injury in a mouse model of MI. This deleterious post-MI phenotype is rescued with genetic mitochondrial CaMKII inhibition; conversely, mice with myocardial and mitochondrial CaMKII overexpression (mtCaMKII) present with severe dilated cardiomyopathy and decreased ATP production. To date, the molecular mechanisms by which mtCaMKII regulates mitochondrial energetics are not fully elucidated. We have identified changes in the activity of enzymes in the mitochondrial electron transport chain and TCA cycle in response to increased CaMKII levels or activity, indicating a novel and critical role in mitochondrial metabolism for this kinase. We are currently mapping the mtCaMKII interactome via liquid chromatography–mass spectrometry (LCMS) and proteomics analysis of both scaffolding interactions with proximity labeling utilizing TurboID technology alongside endogenous protein pulldowns. Additionally, we are identifying novel CaMKII kinase-substrate relationships using an ATP-analogue labeling, in order to identify metabolic enzymes which may be regulated via post-translational modifications by CaMKII. The identification of previously unknown mitochondrial partners for cardiac CaMKII may uncover promising pharmacological targets for cardiovascular therapeutics, particularly in treating the progression of HF.