Title: Obesity and the Sustainability of Calcium Oscillations in Hepatocytes: Explicitly Modeling Mitochondria-associated ER Membranes.

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Abstract Text:

Membrane contact sites between the endoplasmic reticulum (ER) and mitochondria are referred to as mitochondria-associated ER membranes (MAMs) and form calcium (Ca^{2+}) microdomains where more direct ER-mitochondria Ca^{2+} exchange can happen. As reported by Arruda et al. (Nature Medicine, 2014), the upregulation of MAMs and altered Ca^{2+} activities were observed in hepatocytes from genetically obese mice. Through mathematical modeling and simulations, we investigated the role of MAMs in intracellular Ca^{2+} dynamics and the effects of obesity.

We constructed a mathematical model that describes the dynamics of Ca^{2+} concentrations in three compartments: the cytosol, mitochondria, and MAMs, as well as mitochondrial metabolic pathways. The proportions of the ER and mitochondria membrane facing the MAMs were explicitly parameterized in the model, so that we could effectively simulate the upregulation of MAMs.

Model simulations suggest that the degree of MAM formation is negatively correlated with the amplitude of cytosolic Ca^{2+} oscillations, but positively correlated with that of mitochondrial Ca^{2+} oscillations. When the model reflecting the cellular changes associated with obesity was simulated to generate Ca^{2+} oscillations over a wide range of stimulus concentration, the oscillations ceased at a lower stimulus concentration, compared to the oscillations simulated from the model with the control cellular condition. This model simulation predicts that hepatocytes from obese mice exhibit Ca^{2+} oscillations that are less likely to be sustained under higher concentrations of stimulus, compared to those from control mice.