Joint Department of Biomedical Engineering
Marquette University / Medical College of Wisconsin

Announcement of Public Dissertation Defense

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Engineering Hall, Room 323
Marquette University

Xiao Zhang, B.S. - Ph.D. Candidate

Advisor: Said Audi, Ph.D.

ABSTRACT

Thermodynamically-Constrained Computational Modeling of Lung Tissue Bioenergetics and the Effect of Hyperoxia-Induced Acute Lung Injury

Altered lung tissue bioenergetics is an important and early step in the pathogenesis of acute lung injury (ALI), one of the most common causes of admission to medical ICUs. A wealth of information exists regarding the effect of ALI on specific mitochondrial and cytosolic processes in isolated mitochondria, cultured endothelial cell, and intact lungs. However, the interdependence of lung cellular processes makes it difficult to quantify the impact of a change in a single or multiple cellular process(es) on overall lung tissue bioenergetics. Integrating bioenergetics data from isolated mitochondria and intact lung is necessary for determining the functional significance of targeting a specific cellular process for prognostic and/or therapeutic purposes. Thus, the main objective of my dissertation was to develop and validate comprehensive, thermodynamically-constrained models of mitochondrial and lung tissue bioenergetics, and to use these models to predict the impact of ALI-induced changes in mitochondrial and cytosolic processes on lung tissue bioenergetics. For Aim 1, I developed and validated an integrated model of the bioenergetics of mitochondria isolated from rat lungs, which incorporates the major biochemical reactions and transport processes in lung mitochondria. The model provides important insights into the bioenergetics and respiration of lung mitochondria and how they differ from those of mitochondria from other organs. For Aim 2, I developed and validated an integrated computational model of lung tissue bioenergetics. The model expanded the computational model developed under Aim 1 by accounting for glucose uptake and phosphorylation, glycolysis, and the pentose phosphate pathway. The model was then used to gain novel insights on how lung tissue glycolytic rate is regulated by exogenous substrates, and assess differences in the bioenergetics of isolated mitochondria isolated from lung tissue and those of mitochondria in intact lungs. For Aim 3, the models developed under Aims 1 and 2 were used to quantify the impact of previously measured changes in specific mitochondrial processes in a rat model of clinical ALI on lung mitochondrial and tissue bioenergetics. To the best of our knowledge, the two computational models are the first for lung mitochondrial and tissue bioenergetics. These models provide a mechanistic and quantitative framework for integrating available lung tissue bioenergetics data, for testing novel hypotheses regarding the role of different cytosolic and mitochondrial processes in lung tissue bioenergetics and the pathogenesis of ALI, and for identifying potential therapeutic targets for ALI.

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