Identifying components of the mitochondrial electron transport chain that mediate oxygen sensing in the pulmonary circulation: potential therapeutic targets for pulmonary hypertension

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Objective: Identify the subunit(s) of the mitochondrial electron transport chain responsible for oxygen-sensing in the pulmonary vasculature.

Background: The ability to respond to changes in oxygen is mediated by the homeostatic oxygen sensing system, consisting of resistance pulmonary arteries (PA), ductus arteriosus, carotid bodies, and neuroepithelial bodies, functioning together to improve oxygen uptake and delivery. Within the PA, hypoxic pulmonary vasoconstriction (HPV) matches lung perfusion to ventilation, whereas systemic arteries dilate during hypoxia. Mitochondria in pulmonary artery smooth muscle cells (PASMC) serve as redox-sensitive O_2 sensors, modulating vascular tone by releasing reactive oxygen species (ROS) in proportion of alveolar O_2 levels. These ROS control the function of potassium channels (e.g. Kv1.5) and enzymes (e.g. rho kinase). However, the identity of the specific mitochondrial protein(s) responsible for oxygen-sensing remains elusive. Because HPV is unique to PASMC (systemic ASMC dilate during hypoxia), we compared these mitochondria, reasoning the oxygen-sensing components of the mitochondria might be differentially expressed.

Methods: Mitochondria from rat pulmonary and renal artery (RA) SMC were compared via activity assay, micropolarimetry, mass spectrometry, RT-PCR and Western blot. Hydrogen peroxide (H_2O_2) and calcium flux were measured using H_2O_2- and Ca^{2+}-specific probes and confocal microscopy.

Results: Relative to RASMC, PASMC exhibit increased Complex I activity and oxidative metabolism. Seven candidate proteins/subunits have been identified as differentially expressed in PASMC and RASMC, including iron-sulfur subunits of Complexes I and III, and mitochondrial uncoupling proteins. Upon hypoxia, PASMC H_2O_2 levels decrease prior to calcium influx, supporting the theory that decreased H_2O_2 during hypoxia is the cellular signal mediating HPV.

Future directions: Further experiments aim to confirm the identity of the mitochondrial oxygen sensor via knockdown/silencing of candidate proteins. Identification of specific components of the oxygen-sensing system may identify therapeutic targets for diseases of impaired oxygen-sensing, such as pulmonary hypertension and chronic altitude sickness.