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Mitochondrial and Metabolic Effectors from the Aging Placenta May Trigger the Onset of Labor

Abstract

Objective: To elucidate mechanisms underlying the onset of parturition, including a potential new role for mitochondrial (mt) signaling. As most cases of pre-term labor (PTL) have unknown cause, and given the burden of prematurity on neonatal health, this is a high-impact study.

Background: Placental aging may promote labor onset, but specific mechanisms remain elusive. We report new findings that placental mt function is impaired late in gestation, secondary to hypoxia-inducible factor 1 (HIF1) induction, and data from our novel mouse model of PTL supports our hypothesis, that mt effectors of aging from placental trophoblasts drive parturition.

Aim 1: Delineate mechanisms underlying mt changes in trophoblasts following HIF1 induction. Using JAR cell and primary trophoblast models, we will define the relationship between HIF1, mt dysfunction, and inflammation, and test whether interventions targeted at mt function can abrogate the downstream inflammation and make the cells resilient to these agerelated effects.

Aim 2: Test whether mt mechanisms drive parturition in mice. Our preliminary data from Pgc1a knockout mice (lacking a major mt biogenesis gene) show that loss of Pgc1a causes shortening of gestational length. We will use this powerful model to explore the placental mt and metabolic derangements driving the gestational phenotype, and perform rescue experiments with pharmacological interventions targeted at restoring mt health.

We expect to identify a novel pathway linking placental mt dysfunction with specific downstream inflammatory effector molecules driving parturition. These results could be rapidly deployed clinically, as markers for prediction of PTL, for enrichment of trials in PTL for high-risk patients, or as therapeutic targets for this burdensome problem lacking effective interventions.