Child Health Research Institute

University of Nebraska Medical Center

Children's Hospital & Medical Center

The Role of Omega-3 Derived Pro-Resolving Mediators in the Hypertensive Placenta

Authors: Taija Hahka[1], Matt VanOrmer[1], Rebecca Slotkowski[1], Anum Akbar[1], Melissa Thoene[1], Corrine Hanson[2], Sathish Natarajan[3], Srivatsan Kidambi[4], Ann Anderson-Berry[1]

[1]Department of Pediatrics, University of Nebraska Medical Center, Omaha, NE 68198
[2] College of Allied Health Professions, University of Nebraska Medical Center, Omaha, NE 68198
[3] Department of Nutrition and Health Sciences, University of Nebraska-Lincoln, Lincoln, NE 68588
[4] Department of Chemical and Biomolecular Engineering, University of Nebraska-Lincoln, Lincoln, NE 68198

Hypertensive Disorders of Pregnancy (HDP) occur in 1 out of every 10 pregnancies and are a leading cause of maternal and infant mortality worldwide. HDP is characterized by poor placental trophoblast invasion followed by a maternal systemic inflammatory response. Excessive and chronic inflammation results in mitochondrial dysfunction and uncontrolled mitochondrial replication, which could promote placental stiffness. The mitochondrial transcription factor A (*TFAM*) gene is a biogenic controller of mitochondrial DNA replication and may drive uncontrolled mitochondrial function. Omega-3 (n-3) fatty acid-derived specialized pro-resolving mediators (SPMs) promote anti-inflammatory and pro-repair processes; however, the mechanism between SPMs regulating inflammation and mitochondrial function during HDP is unclear. Pregnant women in the United States consume, on average, half the recommended intake of n-3 defined by the World Health Organization. Poor n-3 intake may increase the risk of placental stiffness leading to negative perinatal outcomes like death, preterm birth, and low birth weight. SPMs represent potential therapeutic targets for modulating inflammation and mitochondrial dysfunction. We hypothesize that SPMs mitigate pro-inflammatory cytokine (TNFα) and mitochondrial dysfunction by modulation of *TFAM* and oxygen consumption rates in artificial tissue stiffnesses. Human placental samples of normotensive and hypertensive placenta underwent RNA-sequencing to obtain relative expression of mRNA (n=4 per group). Human-derived trophoblast cells were subjected to pro-inflammatory cytokine (TNFα, 10 ng/mL) or Bio-Engineered Adhesive Siloxane Substrate with Tunable Stiffness (BEASTS) to mimic *in vivo* placental stiffness for 8, 25, and 55 kPa. Resolvin D2 (RvD2, 100nM) was applied as a treatment strategy to mitigate inflammation and mitochondrial dysfunction. Real-Time qPCR was used to measure *TFAM* mRNA relative expression, and Seahorse® was used to measure oxygen consumption rates and ATP production (n=3-4 per group). One-way ANOVA or student t-test was performed. Our RNA-sequencing data showed that *TFAM* is increased in hypertensive human placenta compared to normotensive placenta (5.81 vs. 3.80; p=0.0036). Trophoblasts subjected to TNFα demonstrated an increase in *TFAM* expression levels which was mitigated by treatments with RvD2 (0.0024 vs. 0.0010; p=0.0258). Trophoblasts exposed to 55kPa and treated with RvD2 decreased *TFAM* expression by 2.5-fold (6.7E-06 vs. 2.6E-06; p=0.0021). Seahorse® measurements of trophoblasts exposed to TNFα+RvD2 demonstrated promising trends of improved maximal respiratory rate ranges (TNFα:48-194 vs. TNFα+RvD2:97-231 pmol/min/mg/ml) and ATP mean production (TNFα:7.44 vs. TNFα+RvD2:28.28 pmol/min/mg/ml; p=0.0697). RvD2 exhibits a protective role through modulation of TFAM in the mitochondria of human-derived trophoblasts during inflammatory insult or severe tissue stiffness.