The erythrocyte metabolome in altitude-associated fetal growth restriction

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Introduction: High altitude (>2500 m) increases the incidence of fetal growth restriction (FGR), a leading cause of perinatal mortality and morbidity worldwide. The effect of HA to suppress fetal growth is mainly due to chronic maternal hypoxia and, in turn, insufficient oxygen (O_2) delivery to the uteroplacental circulation. Erythrocytes are central for systemic O_2 transport and rely on the precise control of hemoglobin (Hb)-O_2 affinity by endogenous allosteric modulators such as 2,3-bisphosphoglycerate (2,3-BPG) to maintain efficient O_2 uptake and delivery. The production of 2,3-BPG is regulated in part by metabolic processes and metabolites (e.g., adenosine). In this study, we aimed (1) to determine whether the erythrocyte metabolome is altered in altitude-associated FGR, with a lower abundance of metabolites known to enhance the offloading of O_2 from hemoglobin, and (2) to establish the relationship between prioritized metabolite abundance, fetoplacental hypoxia, and fetal growth. **Methods**: Umbilical venous and arterial blood samples were obtained from FGR cases (*N* = 10) and appropriate for gestational age (AGA) controls (*N* = 12) born to Andean women delivering by Cesarean section and living in La Paz, Bolivia (3600-4100m). Metabolomic profiles were generated by the CU Metabolomics Core using UHPLC-MS and contrasted by FGR status using MetaboAnalyst 5.0. Umbilical plasma erythropoietin and umbilical venous and arterial blood gases (pO_2, pCO_2) were measured as indices of fetal hypoxia. Using Spearman correlation, we determined the relationship between metabolite abundance and indices of fetal growth and oxygenation. False discovery rate-adjusted *p* values < .05 were considered statistically significant. **Results:** We identified 76 metabolites differing in abundance by FGR status; among these, adenosine abundance was lower in FGR versus AGA. Metabolic pathways differing by FGR status included purine metabolism; aminoacyl-tRNA and arginine biosynthesis; alanine, aspartate and glutamate metabolism. Metabolite associations with estimated fetal weight percentile (110 metabolites), erythrocyte count (59 metabolites), and umbilical arterial or venous pO_2 (9 metabolites) were also identified. **Conclusion:** In highland Andeans, we identified unique erythrocyte metabolite profiles, including suppressed adenosine abundance and altered purine metabolism in FGR. We speculate that the equilibrium between erythrocyte and extracellular adenosine plays a central role in fetal O_2 delivery and growth by balancing O_2 release and vascular function.