The erythrocyte metabolome in altitude-associated fetal growth restriction

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Introduction

- High altitude (HA, >2500 m) increases the incidence of fetal growth restriction (FGR) due, in part, to maternal hypoxia and insufficient uteroplacental O_2 delivery.
- 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).

Objectives

- Characterize the fetal erythrocyte metabolome in HA FGR cases and appropriate for gestational age (AGA) controls
- Establish the relationship between prioritized metabolites for fetoplacental hypoxia and fetal growth

Methodology

- Umbilical venous blood samples were obtained from FGR cases (N = 10) and AGA controls (N = 12) born to Andean women delivering by Cesarean section and living in La Paz, Bolivia (3600-4100m).
- Umbilical venous and arterial blood gases (PO_2, PCO_2) were measured as indices of fetal hypoxia.
- Metabolomic profiles were generated using UHPLC-MS and contrasted by FGR status using MetaboAnalyst 5.0.
- 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 and Discussion

1 Maternal pre-gravid weight was higher in FGR. Maternal height, parity, ancestry, and education level was similar between groups. Birth weight, head and chest circumference were lower in FGR, while hematocrit and hemoglobin levels were greater.

Maternal Characteristics

Variable	AGA, n = 12	FGR, n = 10	p value
Weight, pre-gravid, kg	58.2 ± 10.9	66.0 ± 13.1	.02
Height, m	1.57 ± 0.06	1.55 ± 0.06	.37
Parity, no. births	1.4 ± 0.8	0.7 ± 1.1	.09
Ancestry, %			
Aymara	5/11	5/10	NS
Mestiza	5/11	5/10	NS
Other	1/1	0/10	NS
Secondary education or above, %	12/12	9/10	NS

Newborn Characteristics

Variable	AGA, n = 12	FGR, n = 10	p value
Birth weight, g	3311 ± 554	2184 ± 235	< .001
Gestational age, wks	38.3 ± 1.7	36.8 ± 2.2	.10
Length, cm	48.0 ± 1.9	45.5 ± 3.0	.03
Head circumference, cm	34.8 ± 1.4	31.7 ± 1.1	< .001
Chest circumference, cm	33.7 ± 2.2	28.6 ± 1.5	< .001
Cord hematocrit, %	48.6 ± 6.9	56.7 ± 7.3	.02
Cord Hb, g/dL	16.1 ± 2.3	18.7 ± 2.4	.02

2 Sixty-seven metabolites, representing key pathways, differed by FGR status. These included:

- aminoacyl-tRNA biosynthesis
- purine metabolism
- arginine biosynthesis

Select nucleotide metabolites, metabolites involved in glycolysis and the TCA cycle, and amino acids differing by FGR status are shown in Figure 1. Among these is reduced adenosine in FGR.

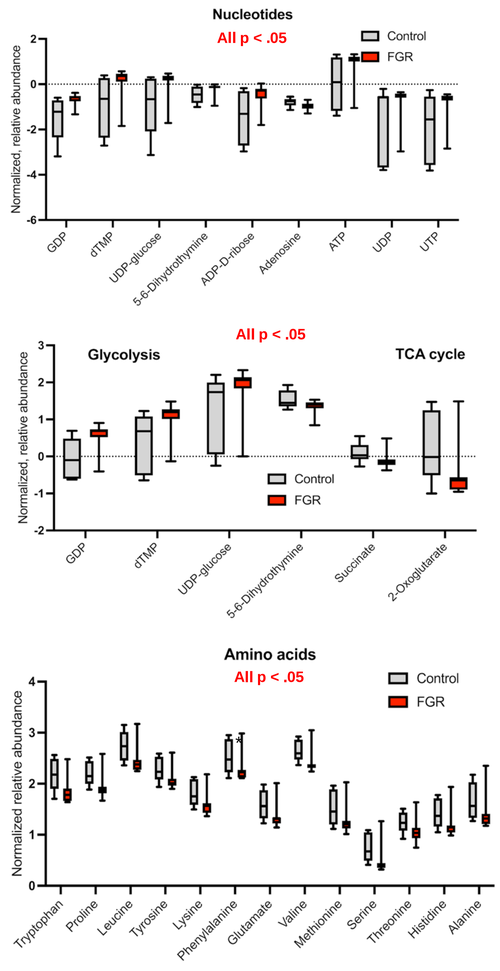
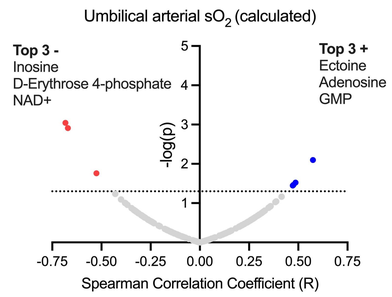
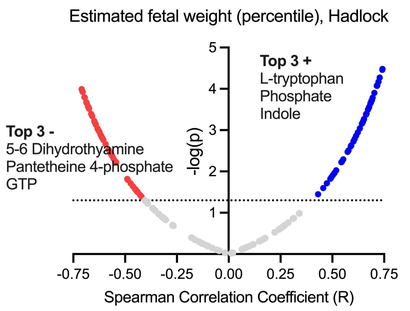


Figure 1. Box and whisker plots of select metabolites that differed by FGR status. Boxes represent the median, upper and lower quartile. Whiskers represent the data range (upper and lower extreme value).

Results and Discussion Continued

3 Associations between metabolite abundance and key outcomes including indices of fetal oxygenation, fetal growth, and erythropoiesis were identified (Figure 2).





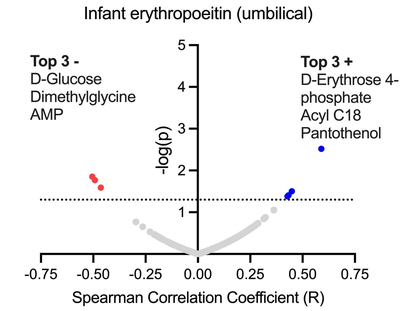


Figure 2. Correlation plots for metabolites and key outcome measures. Blue, red, and gray dots indicate metabolites positively, negatively, or not significantly associated with the outcome, respectively.

Conclusions

- In highland Andeans, we identified unique erythrocyte metabolite profiles, including suppressed adenosine abundance and altered purine metabolism in FGR.
- These results indicate a potential role for erythrocyte metabolism in reduced fetal oxygenation and FGR at high altitudes.
- We speculate that the equilibrium between erythrocyte and extracellular adenosine plays a central role in fetal O_2 delivery via its role in balancing O_2 release and vascular function.

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