Integrated multiomics reveals PGC-1α-driven metabolic remodeling in mouse placenta

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LC-TIMS-MS/MS Multiomics

Modern LC-MS/MS systems are typically dedicated to either proteomics or metabolomics. However, these data types are inherently complementary: metabolomics provides a direct functional readout of biochemical activity, while proteomics identifies the enzymatic drivers behind those metabolic shifts.

The placenta is a metabolically intense organ essential for fetal development and serves as an ideal model for exploring complex metabolic reprogramming. Here, we investigate the role of PGC-1α, a master transcriptional coactivator whose dysregulation creates a profound metabolic phenotype that alters mitochondrial biogenesis and cellular bioenergetics. Using an integrated, parallel split-sample workflow, we profile matched placental lysates and interstitial fluid (IF) across a cohort of 35 placentas from PGC-1α overexpression (OE, n=3 mice) and wildtype (n=4 mice) lines. By mapping enzymatic and metabolic signatures associated with PGC-1α deficiency in both the tissue and its microenvironment, we aim to uncover molecular mechanisms that underpin severe placental diseases, such as preeclampsia.

Fig. 1 | Separating mouse fetus from the placenta.

Metabolomics

Placentas were extracted with hot ethanol spiked with 17 $^{13}C/^{15}N$-labeled amino acids. Analytes were separated on a Bruker BioAQ column (100 x 2.1 mm) using 0.1% formic acid in water/acetonitrile. TIMS-LC-MS/MS data were acquired on a timsMetabo using DDA-MoRE acquisition mode (Fig. 2). Data were processed using MetaboScape 2026.

In placental lysates, significant within-mother heterogeneity was observed with placentas from different mothers clustering closely together in a PCA plot (Fig. 3a). In placental interstitial fluid, adipoylcarnitine was observed to accumulate in PGC-1α OE mice. This finding indicates that in healthy placenta, PGC-1α regulates β fatty acid oxidation. When highlighting all acylcarnitines over the volcano plot, several were found to be enriched in the IF (Fig. 3b, green dots)

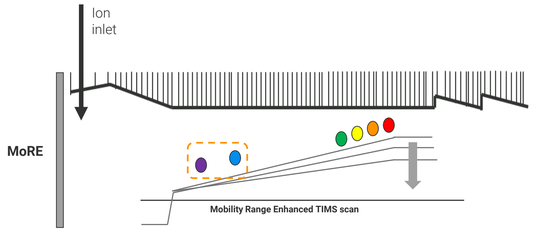

Fig. 2 Concept of Mobility Range Enhancement (MoRE) acquisition mode allowing for higher ion capacity for proteomics and broader mobility range for metabolomics.

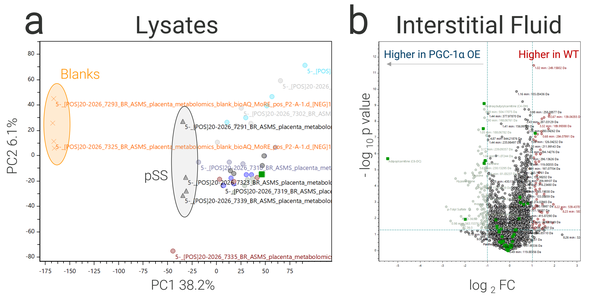

Fig. 3 | Metabolomics analysis in mouse placenta. **a)** Principal component analysis in placental lysate. Samples mostly separate along the *x*-axis with blanks clustering separately. Samples from the same litter are colored with the same colors. **b)** Differential analysis in interstitial fluid comparing WT to PGC-1α OE. The green overlay represents acylcarnitines.

Proteomics

Proteins were recovered from lyophilized tissue, denatured in the presence of protease inhibitors, reduced, alkylated, and cleaned with SP3 beads prior to overnight trypsin digestion and C18 cleanup. Peptides (100 ng) were separated on a IonOpticks column (250 x 0.15 mm) using a 0.1% formic acid water/acetonitrile gradient. TIMS-LC-MS/MS data were acquired in DIA-MoRE (Fig. 2) mode and processed using DIA-NN.

We identified 6,431 protein groups in placental lysates and 1,180 in interstitial fluid samples. Comparative analysis revealed 20 differentially abundant metabolic enzymes linked to energy homeostasis between PGC-1α overexpression mice and wildtype mice in intercellular material (Fig. 4a and Table 1). In the interstitial fluid, only one metabolic signaling protein was identified: Q08652, Retinol-Binding Protein 2, a metabolic gatekeeper upstream of nuclear signaling and mitochondrial reprogramming (Fig. 4b).

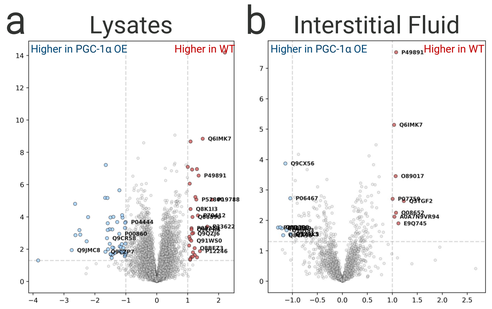

Fig. 4 | Proteomics differential analysis in mouse placenta. **a)** WT vs. OE lysates **b)** WT vs. OE IF.

Uniprot ID	Log2FC	p value	Description
Q6IMK7	1.481249	1.42E-09	Apolipoprotein-associated protein
P49891	1.350307	2.75E-07	Phosphoglycerate kinase
P52800	1.274921	8.27E-06	Pyruvate kinase
P19788	1.781036	8.34E-06	Glucose-6-phosphate isomerase
Q8K1I3	1.089	3.24E-05	Aldolase
P70412	1.324928	8.01E-05	Malate dehydrogenase
Q06890	1.15182	0.000101	Enolase
P04444	-1.00773	0.000207	GAPDH
P33622	1.628967	0.000394	Fatty acid-binding protein
P08228	1.122387	0.000494	Superoxide dismutase
Q9EPR4	1.121625	0.000598	Lipid metabolism-associated protein
Q9QZJ6	1.141868	0.00107	Oxidoreductase metabolic enzyme
P00860	-1.21235	0.001106	Acyl-CoA dehydrogenase
Q9CR58	-1.61132	0.00208	Mitochondrial metabolic protein
Q91WS0	1.112703	0.002959	Lipoprotein component
Q8BFZ3	1.220489	0.00862	Oxidoreductase
Q9JMC8	-2.75044	0.011297	Mitochondrial enzyme
P12246	1.391417	0.013241	Creatine kinase
Q9CZP7	-1.66179	0.014276	Mitochondrial protein
Q9D7S7	1.16562	0.015787	Lipid metabolism protein

Table 1 | Descriptions of all metabolic enzymes found altered in PGC1α overexpression placentas.

Multiomics integrated landscape of placental metabolism

All identified metabolites and proteins were visualized over core metabolic pathways (Fig. 5). We observed that many pathways, such as the TCA cycle, urea cycle, and nucleotide synthesis, have complementary metabolomics and proteomics coverage, allowing for the determination of differential pathway activity.

We observed general downregulation of TCA cycle and glycan synthesis and upregulation in fatty acid oxidation in PGC1a overexpression lines, indicating a metabolic shift from sugar to fatty acid metabolism.

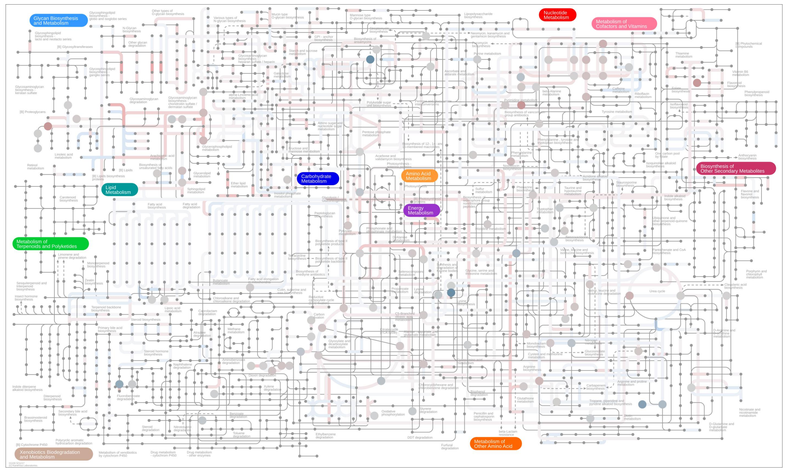

Fig. 5 | iPath3 overlay of metabolomics (nodes) and proteomics (edges) results. Red colors indicate higher abundance in wildtype samples and blue colors indicate higher abundance in PGC1α overexpression samples.

Summary

- timsMetabo workflow enables multiomics analyses with minimal downtime between acquisition modes, completing total data collection in under two weeks.
- Significant biological variation between placentas from the same mother; placenta functions as a highly individual organ.
- Proteomics analysis recovers metabolic enzymes known to be essential to placental function.
- Combining metabolomics and proteomics provides a synergistic biological view that is more informative than the sum of its individual parts.
- We find PGC1α overexpression to shift metabolism from oxidative phosphorylation to fatty acid oxidation

Multiomics TIMS-LC-MS/MS

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