Metabolomics and ^{13}C Glucose Flux in YAP-Mediated Compensatory Hypertrophy under Pressure Overload

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Our role: High-resolution U-^{13}C glucose stable-isotope tracing and metabolic flux analysis of glycolytic and TCA cycle intermediates in cardiac tissues.

Background

Pressure overload triggers compensatory cardiac hypertrophy, yet inadequate adaptation leads to heart failure.

YAP activation is transient and protective: reduced YAP blunts hypertrophy but worsens function.

Given YAP's link to Warburg-like glycolysis, a key question is whether metabolic reprogramming underlies this compensation.

Research Question

Does YAP drive a Warburg-like aerobic glycolysis program to support compensatory cardiac hypertrophy?

Hypothesis

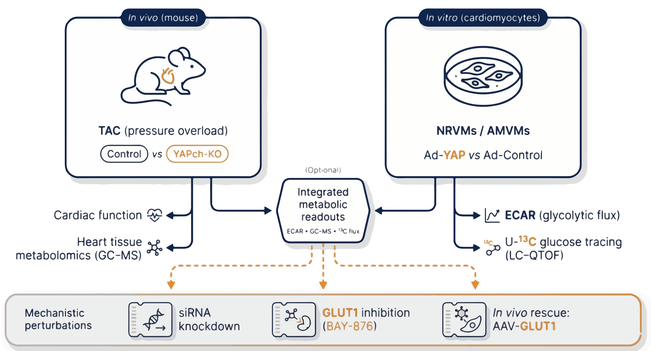
YAP promotes compensatory hypertrophy by activating GLUT1-dependent aerobic glycolysis and rerouting glucose carbon into anabolic and anaplerotic pathways.

Objectives

1. Test whether YAP is required for glycolytic activation under pressure overload.
2. Profile YAP-driven metabolite changes and glucose carbon flux using metabolomics and U-^{13}C glucose tracing.
3. Validate GLUT1-dependent glycolysis as a key mechanism.

Study Design

In vivo TAC model (control vs YAPch-KO) plus cardiomyocyte models (NRVMs/AMVMs, Ad-YAP vs control), integrating ECAR, GC–MS metabolomics, and U-^{13}C glucose LC–QTOF tracing with mechanistic perturbations (siRNA, BAY-876, AAV-GLUT1 rescue).

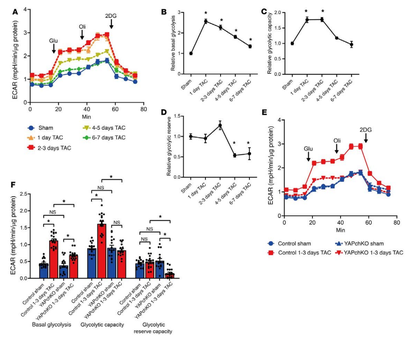


Results

Key Finding 1 —YAP is required for glycolytic activation under pressure overload

Acute pressure overload activates glycolysis in the heart, and this response depends on endogenous YAP.

- TAC increases basal glycolysis and glycolytic capacity in control hearts.
- TAC-induced increases in these glycolytic parameters are significantly attenuated in YAPch-KO hearts.

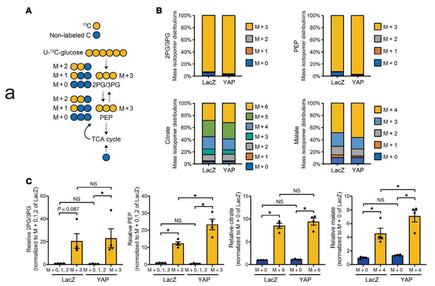


YAP is required for TAC-induced glycolytic activation (basal glycolysis and glycolytic capacity increase in controls but are blunted in YAPch-KO).

Key Finding 2 — YAP rewires central carbon metabolism and increases glucose-derived flux

Metabolomics and U-^{13}C glucose tracing support a Warburg-like program under YAP activation.

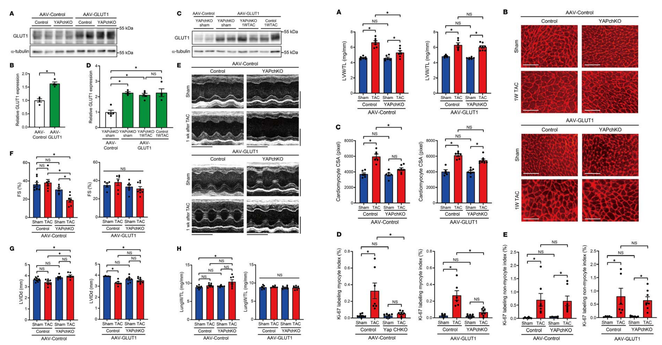
- Central-carbon intermediates shift toward downstream glycolysis and anaplerotic/TCA nodes.
- ^{13}C labeling of PEP (M+3) and malate (M+4) increases, indicating higher glucose-derived carbon flow.



^{13}C tracing confirms increased glucose-derived flux under YAP activation (higher PEP M+3 and malate M+4).

Key Finding 3 — GLUT1-dependent glycolysis is essential for YAP-mediated hypertrophy and cardioprotection

In cardiomyocytes, GLUT1 inhibition suppresses YAP-driven glycolysis and hypertrophy, while cardiac GLUT1 restoration improves outcomes in YAP-deficient hearts after TAC.



Cardiac GLUT1 restoration improves outcomes in YAP-deficient hearts after TAC, supporting GLUT1-dependent cardioprotection.

Our Contribution (Creative Proteomics)

U-^{13}C glucose stable-isotope tracing with high-resolution LC–QTOF metabolomics to quantify isotopomer distributions of glycolytic and TCA-cycle intermediates in cardiomyocytes.

Core readouts delivered

- Isotopomer patterns (M+0…M+n) and fractional labeling
- Glucose-derived labeling of key nodes (e.g., PEP, malate)
- QC-checked peak integration and data tables suitable for publication figures

Proposed Model

Under pressure overload, YAP activation enhances GLUT1-dependent aerobic glycolysis and increases glucose-derived carbon flux into central-carbon metabolism, supporting compensatory hypertrophy and preserving cardiac function.

Conclusion & Significance

Our study reveals that YAP acts as a metabolic "master switch" during cardiac stress. By orchestrating a GLUT1-mediated glycolytic shift, YAP ensures the heart meets the massive biosynthetic and energy demands required for compensatory hypertrophy, thereby preventing the transition to heart failure. This identifies the YAP-GLUT1 axis as a promising therapeutic target for metabolic intervention in cardiomyopathies.

Why Choose Creative Proteomics

- Audit-ready methods & QC criteria

Clear parameters, integration rules, isotope correction assumptions, and acceptance thresholds.

- Isotopomer integrity checks (M+0…M+n)

Peak identity verification and interference screening to reduce mis-assignment risk.

- Central-carbon practical controls

Workflow safeguards for labile glycolytic/TCA intermediates, carry-over, and batch comparability.

- Reviewer-friendly reporting

Results packaged to connect metabolite pools with flux evidence without over-interpretation.

Working on cardiac, metabolic, or stress-response models? Let's build a metabolomics + ^{13}C glucose tracing plan that answers your mechanism questions.

Web: www.creative-proteomics.com

Email: info@creative-proteomics.com

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