Untargeted Metabolomics Reveals Redox-Gated Stress Resolution via Caspase–FASN Cleavage

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Background & Objective

Organisms face diverse stressors (ER, osmotic, ROS). Beyond mounting stress programs, how do they sense that stress has been resolved and coordinately dial down responses?

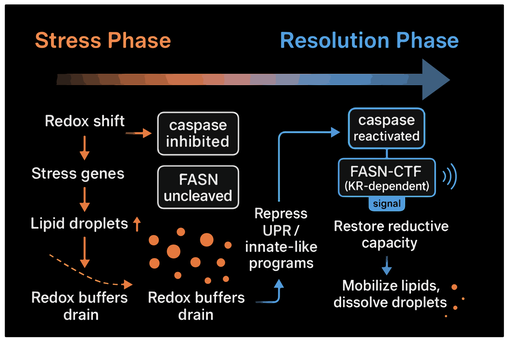
This study discovers that limited caspase cleavage of FASN generates a C-terminal fragment (FASN-CTF) that acts as a global stress-resolution cue.

Core Mechanism

During stress: Oxidizing environment → caspase (CED-3/3) is inhibited → FASN remains full-length → redox buffer depletes, lipid droplets accumulate, stress programs remain elevated.

After mitigation: Redox is restored → caspase reactivates → proteolytic generation of FASN-CTF → non-cell-autonomous downregulation of stress genes, remodeling of lipid metabolism, mobilization of lipid droplets (LDs).

Key domain: KR domain activity in FASN-CTF is required for suppression of stress responses.



Key Findings

FASN-CTF suppresses ER/osmotic/ROS stress markers and reduces stress-induced LD accumulation.

Function is independent of palmitate biosynthesis (supplementation does not rescue heightened responses).

Cleavage-resistant fasn-1(D1593E) mutants phenocopy ced-3(−), confirming caspase-FASN coupling in stress control.

FASN processing also observed in well-fed (not fasted) mouse liver, supporting conservation across species.

Contact Us

Discovery Matabolomics Profiling at A Glance

Comparative coverage: genotypes × stress conditions (~6 replicates).

Differential signatures: hundreds of metabolites altered; ced-3(−) & FASN-D1593E share a large co-directional overlap.

Pathway focus: glutathione/redox & sulfur amino acids enriched.

Multivariate PCA: stress (PC1) vs genotype (PC2) cleanly separated.

PCA separates stress from genotype

- PC1 reflects stress treatments (ER, osmotic, ROS).
- PC2 distinguishes genotypes at baseline but converges after stress.
- Interpretation: ced-3(−) and fasn-1(D1593E) mutants display a pre-stressed metabolic profile even without stress.

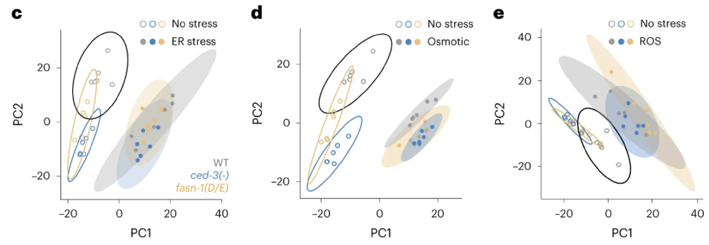


Fig. 3c–e (PCA): PC1 = stress treatment, PC2 = genotype separation at baseline.

Pathway enrichment highlights redox

- Glutathione and redox adaptation pathways rank highest (FDR < 0.1).
- Additional enrichment includes carnitine and β-alanine metabolism, indicating altered substrate handling and antioxidant balance.

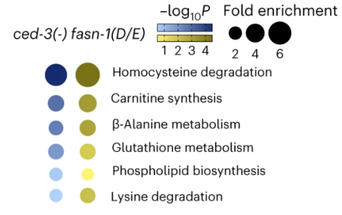


Fig. 3f Pathway enrichment (MetaboAnalyst, SMPDB): ced-3(−) and fasn-1(D/E) mutants vs WT.

Glutathione pathway: oxidized baseline

- GSH/homocysteine metabolites depleted in ced-3(−) and fasn-1(D1593E) under no stress.
- This mirrors WT under stress, supporting oxidative gating of caspase and FASN cleavage.

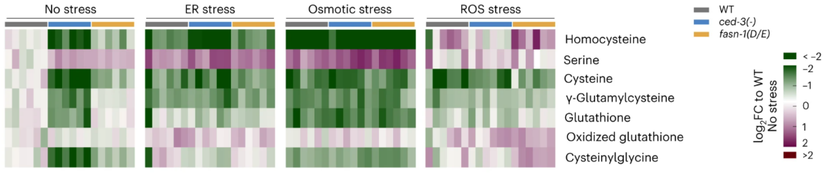


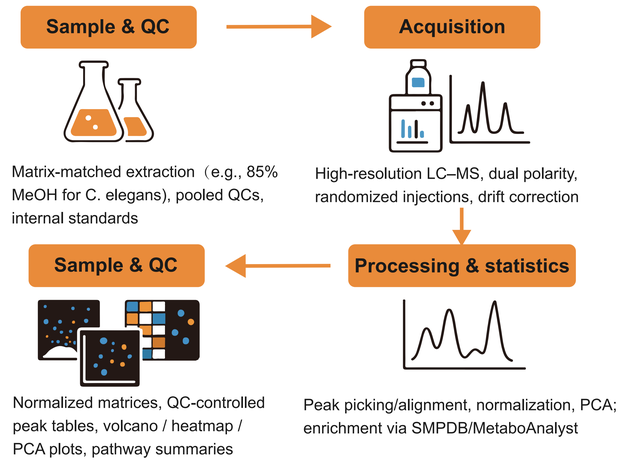
Fig. 3g Heat map of detected metabolites in glutathione pathway.

How Creative Proteomics Helped

Our Contributions in This Study

- Implemented a rigorous LC–MS pipeline with pooled QCs, internal standards, and replicate validation.
- Supplied publication-ready data packages (raw + processed + QC report) compliant with journal standards.
- Ensured results were analysis-ready for integration with transcriptomics and imaging.

Untargeted Metabolomics Service Workflow



Why Choose Creative Proteomics

Scale & experience: >1,200 metabolomics projects delivered across human, animal, plant, and microbial systems.

Reproducibility: >90% of datasets with QC median RSD < 15% (pooled QC).

Publication impact: Data supporting >300 peer-reviewed papers (incl. *Nature Metabolism*, *Cell Metabolism*, *Nat Commun*).

Coverage: >2,000 metabolites detectable across redox, lipid, amino-acid & energy pathways（dual-polarity libraries）.

Interested in Profiling Metabolism in Your System?

Contact us to discuss how untargeted LC–MS metabolomics can profile global metabolite changes, reveal pathway-level insights (redox, lipid, energy).

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