nature research

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Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work we publish. This form is published with all life science papers and is intended to promote consistency and transparency in reporting. All life sciences submissions use this form; while some list items might not apply to an individual manuscript, all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

   Describe how sample size was determined.

   Sample size was based on experience in prior studies and sized to allow significance in biologically relevant effect sizes.

2. Data exclusions

   Describe any data exclusions.

   No data that was deemed technically accurate was excluded.

3. Replication

   Describe whether the experimental findings were reliably reproduced.

   Findings were reproduced with multiple experiments. One exceptions was large flux modeling work, however the underlying observation of glucagon-stimulated glutamine utilization was replicated multiple times in metabolic flux studies

4. Randomization

   Describe how samples/organisms/participants were allocated into experimental groups.

   Animals were randomized based on blood glucose.

5. Blinding

   Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

   For in vivo studies researchers were blinded to animal groups.

   Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

   For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or the Methods section if additional space is needed).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒	A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly.
☐	☒	A statement indicating how many times each experiment was replicated
☐	☒	The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒	A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒	The test results (e.g. *p* values) given as exact values whenever possible and with confidence intervals noted
☐	☒	A summary of the descriptive statistics, including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒	Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	N/A

For all studies, we encourage code deposition in a community repository (e.g. GitHub). Authors must make computer code available to editors and reviewers upon request. The *Nature Methods* guidance for providing algorithms and software for publication may be useful for any submission.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	There are no restrictions on the materials used in this manuscript

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	p1756 IP3R - Cell Signaling (#8548) - based on molecular weight and PKA stimulation IP3R - Cell Signaling (#8568) based on molecular weight pS133 CREB - Cell Signaling (#9198) - based on PKA responsiveness and molecular weight CREB - Cell Signaling (#9197) based on molecular weight pY1150/1151 IR - Cell Signaling (#3024) based on response to insulin IR-beta - Cell Signaling (#3025) based on molecular weight pS473 Akt - Cell Signaling (#4060) based on response to insulin Akt - Cell Signaling (#4691) based on molecular weight GAPDH -Cell Signaling (#5174) based on molecular weight beta-Actin - Cell Signaling (#3700) based on molecular weight PFKFB1 - AbCam (ab71625) - based on molecular weight GLS2 - Sigma aldrich (HPA038608) based on molecular weight and loss of signal in knockout animals pS33 PFKFB1 - Cell Signaling (custom) - based on molecular weight and glucagon stimulation

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	Immortalized human hepatocyte cell line
b. Describe the method of cell line authentication used.	morphology
c. Report whether the cell lines were tested for mycoplasma contamination.	Lines were not tested for mycoplasma
d. If any of the cell lines used in the paper are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	N/A

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.	All mouse studies were performed on male animals of the C57bl/6 strain. Animals were aged between 8-20 weeks old at the time of study.

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.	N/A