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☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but 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.

No sample size calculations were performed. Experiments were performed with three replicates for each treatment group in order to observe variance. Experiments were performed three times to ensure reproducibility and accuracy.

2. Data exclusions

Describe any data exclusions.

No exclusions

3. Replication

Describe whether the experimental findings were reliably reproduced.

All attempts at replication were successful

4. Randomization

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

Prior to beginning an experiment, cells were seeded/allocated into wells in the same manner for each sample group. When an experiment was commenced, groups of cells were allocated into treatment groups without pattern or bias. This ensured that each treatment group in an experiment were identical (within the inherent variation caused by cell seeding).

5. Blinding

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

No Blinding was used

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 in 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 clear description of 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.	Prism 7 was used for line-fitting, FlowJo 10.1 was used for flow cytometry analysis, Topspin and MestreNova were used for NMR analysis, Compound Discoverer was used for MS phospholipid analysis.

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

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.	Unique materials used in this study (RSL3, FINO2, FINO2 analogues, deuterated arachidonic acids) were synthesized by the authors and are available upon reasonable request. All other reagents were obtained commercially.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	The antibody for Gpx4 was obtained commercially from abcam (abcam, #ab125066); anti-GAPDH was obtained commercially from Santa Cruz biotech # sc-47724; anti-Ferritin Light Chain was obtained commercially from Santa Cruz biotech #sc-390558; anti-IRP2 was obtained commercially from Nous Biology #NB1001798; anti-Transferrin receptor 1 was obtained commercially from Cell Signaling #13113; anti-Actin was obtained commercially from Cell Signaling #D18C11; anti-alpha-tublin was obtained commercially from Santa Cruz biotech #sc-32293. All antibodies were used without further validation.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	HT-1080, BJ-hTERT, and CAKI-1 were obtained from ATCC; BJ-eLR cells were donated from the lab of William Han at the Dana Farber Cancer Institute.
b. Describe the method of cell line authentication used.	None of the cell lines have yet been identified
c. Report whether the cell lines were tested for mycoplasma contamination.	Cells were tested for mycoplasma pior to used with a PCR-based kit (Sigma). Cells were considered mycoplasma-free as no mycoplasma DNA amplified
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	No lines from this database were used in this study

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.	None used in this 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.	None used in this study