The unfolded protein response of the endoplasmic reticulum supports mitochondrial biogenesis by buffering non-imported proteins

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Editor-in-Chief: Matthew Welch

Transaction Report:

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. The original formatting of letters and referee reports may not be reflected in this compilation.)

RE: Manuscript #E23-05-0205
TITLE: "The unfolded protein response of the endoplasmic reticulum supports mitochondrial biogenesis by buffering non-imported proteins"

Dear Dr. Boos,

Thank you for submitting your manuscript and associated materials for consideration for our special issue on Protein Quality Control. I've thoroughly read the reviewers' comments, your responses and the revised manuscript and would be happy to accept a revised version with changes as outlined in the latest rebuttal letter. For editorial clarity, here are the specific points I consider most important.

1. The ER localisation of endogenous Oxa1 is very hard to see and to my mind detracts from the strong split-GFP experiments. I suggest you move Figure 3a to the supplement.

2. I like the DTT halo assay and suggest you retain it in the main manuscript. I suggest delineating the region of increased growth with a square bracket rather than the arrow, which is a bit vague. A square bracket spanning the width of the growth ring should highlight the region better for readers not familiar with halo assays.

3. I suggest you include the R4 experiment that shows Hac1i expression doesn't rescue clogger-associated growth defects. I think this is wise for the sake of transparency. My conclusion is that UPR-ER is already induced in these cells, so any protective effect is already there. Adding additional Hac1 doesn't further rescue. This could be as a supplement, but I think the data are nice.

4. I'm agnostic on the EndoH experiment - perhaps it's wise to move it to the supplement as both remaining critical reviewers suggest.

Sincerely,
Elizabeth Miller
Monitoring Editor
Molecular Biology of the Cell

Dear Dr. Boos,

The review of your manuscript, referenced above, is now complete. The Monitoring Editor has decided that your manuscript requires minor revisions before it can be published in Molecular Biology of the Cell, as described in the Monitoring Editor's decision letter above and the reviewer comments (if any) below.

A reminder: Please do not contact the Monitoring Editor directly regarding your manuscript. If you have any questions regarding the review process or the decision, please contact the MBoC Editorial Office (mboc@ascb.org).

When submitting your revision include a rebuttal letter that details, point-by-point, how the Monitoring Editor's and reviewers' comments have been addressed. (The file type for this letter must be "rebuttal letter"; do not include your response to the Monitoring Editor and reviewers in a "cover letter.") Please bear in mind that your rebuttal letter will be published with your paper if it is accepted, unless you have opted out of publishing the review history.

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To submit the rebuttal letter, revised version, and figures, please use this link (please enable cookies, or cut and paste URL):
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Sincerely,

Eric Baker
Journal Production Manager
MBoC Editorial Office
mbc@ascb.org

Point-by-point response to the reviewers' comments

1. The ER localisation of endogenous Oxa1 is very hard to see and to my mind detracts from the strong split-GFP experiments. I suggest you move Figure 3a to the supplement.

We moved this Figure panel to the supplements as requested (now Supplementary Figure 5A).

2. I like the DTT halo assay and suggest you retain it in the main manuscript. I suggest delineating the region of increased growth with a square bracket rather than the arrow, which is a bit vague. A square bracket spanning the width of the growth ring should highlight the region better for readers not familiar with halo assays.

As suggested, we have retained this figure panel in the main manuscript and delineated the region of interest by a square bracket to make it easier to see.

3. I suggest you include the R4 experiment that shows Hac1i expression doesn't rescue clogger-associated growth defects. I think this is wise for the sake of transparency. My conclusion is that UPR-ER is already induced in these cells, so any protective effect is already there. Adding additional Hac1 doesn't further rescue. This could be as a supplement, but I think the data are nice.

We have included these data now as Supplementary Figure 5E, alongside a schematic depiction of the expression system used (Supplementary Figure 5D) and statistical analysis of the data (Supplementary Figure 5F). We have included a description and interpretation of the data in the results section of the manuscript (lines 330-333).

4. I'm agnostic on the EndoH experiment - perhaps it's wise to move it to the supplement as both remaining critical reviewers suggest.

We have moved the figure panel to the supplement as suggested (now Supplementary Figure 7C). We have also performed topology prediction on Oxa1 to assess whether the potential glycosylation sites are likely to be exposed to the ER lumen (when localized to the ER) and found agreement of all nine prediction algorithms for luminal localization of the first two glycosylation sites. We have visually highlighted this in Supplementary Figure 7B and explained the prediction method in the Methods section.

RE: Manuscript #E23-05-0205R
TITLE: "The unfolded protein response of the endoplasmic reticulum supports mitochondrial biogenesis by buffering non-imported proteins"

Dear Dr. Boos:

I am pleased to accept your manuscript for publication in Molecular Biology of the Cell.

Sincerely,
Elizabeth Miller
Monitoring Editor
Molecular Biology of the Cell

Dear Dr. Boos:

Congratulations on the acceptance of your manuscript! Thank you for choosing to publish your work in Molecular Biology of the Cell (MBoC).

Within 10 days, an unedited PDF of your manuscript will be published on MBoC in Press, an early release version of the journal. The date your manuscript appears on this site is the official publication date.

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We look forward to publishing your paper in MBoC.

Sincerely,

Eric Baker
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