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Understanding the mammalian TRAP complex function(s)

Antonietta Russo

Article citation details
Open Biol. **10**: 190244.
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Review timeline

Original submission:	10 October 2019
1st revised submission:	3 February 2020
2nd revised submission:	14 April 2020
Final acceptance:	23 April 2020

Note: Reports are unedited and appear as submitted by the referee. The review history appears in chronological order.

Review History

RSOB-19-0244.R0 (Original submission)

Review form: Reviewer 1

Recommendation
Reject – article is not of sufficient interest (we will consider a transfer to another journal)

Do you have any ethical concerns with this paper?
No

Comments to the Author
In this manuscript the author reviewed the current knowledge of TRAP complex, an heterotetrameric complex associated to the translocon. The author revised the structural information that appeared in the last years, basically thanks to cryo-EM and cryo-ET data, and link this information to possible functions of the TRAP complex. General comment followed by specific comments/criticisms are below.

General:
The review includes important errors and omissions that significantly complicates reading. Figures are poorly informative and with very low quality (at least as included in the revised pdf).

The author stated as Tab. (Tables, I assume) images than to me look more like 'Figures' than actual 'Tables'.
Tab. 6 is missing.
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References need profuse curation.
Abbreviations list is required.

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1- Abstract. The first sentence can be misinterpreted. Together, translocated into the ER lumen and ER inserted proteins represent about one-third of the proteome. As written, it is a bit confusing, please clarify.
2- Abstract. The following sentence is either difficult to understand or incorrect: "…however, research has consistently shown a lack of understanding about the role(s) of some of its components. TRAP complex is involved in co-translational translocation, unfolded protein response, ERAD pathways, and glycosylation disorder (ssr4 CDG), but its role in not unknown." Please rephrase.
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6- Fig. 2: explain what the yellow, green and black lines represent in the legend.
7- Fig. 3 is not informative. Please, produce a caption of the TRAP complex using the appropriate PDB codes.
8- Tab. 1-6 appear to be just screenshots (webpages should be mentioned), very low quality and poorly informative images. At least the transmembrane regions should be highlighted, as well as the cytosol and ER lumen exposed loops.
9- Page 5, last paragraph is dedicated to type I membrane proteins, please mention 'type I' explicitly. At the end of the paragraph it should be referred to Tab. 5.
10- Fig. 4 is a cartoon, if the author wants to show the structure, an appropriated caption should be provided, for instance to highlight rpl38 protein as mentioned both in the text and in the figure legend.
11- Page 8: TRAM has also been crosslinked to nascent chains with more than 100 residues. Then, this fact cannot be argued as a differential feature between TRAM and TRAP. Actually, TRAM deserves a clearer description.
12- Page 8: "TRAM also by crosslinking experiments, seems to be involved in viral TM protein integration into the ER, each segment of the chain is before associated with Sec61 α and then with TRAM (44)."
Ref. 44 that deals with TRAP is not correct, the experiments described where published elsewhere. Please, place the appropriate reference.
13- From reference 73 up to the end the literature is totally inconsistent, and its correctness cannot be checked. Please, revise it carefully.
14- Figs. 6 and 7, again with poor quality, they are not very informative. If maintained, both should be significantly improved, and STRING consortium acknowledged (Fig. 6).
15- Page 11. The non-canonical EF-domain at the N-terminus of TRAPalpha is not shown in Tab. 6, which actually is devoted to TRAPdelta, but Tab. 7.
16- Last paragraph: where are Tab. 11-12?
17- Page 12. Sec62 should be introduced and properly spelled (line 2).
18- Page 13 last paragraph it refers to Tab. 8, I guess.

Review form: Reviewer 2

Recommendation
Major revision is needed (please make suggestions in comments)

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No

Comments to the Author
The manuscript covers a topic that would be interesting to a general readership. However in its present form it is of insufficient quality.

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According to title and abstract, the aim of the manuscript is to discuss the function of the mammalian TRAP and therefore it refers generally to the mammalian translocon with its central component, the Sec61 complex. However, many citations refer to work done with prokaryotic organisms. This may be confusing for readers not familiar with the field, especially as the functional homology between the translocon in the mammalian ER and the translocon in the plasma membrane in prokaryotic organisms was not introduced.
In several cases, statements are supported not by citing original literature but other reviews. In other cases the citation is not directly linked to the information provided.
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"…and the SP is functionally distinct and optimized for the mature protein sequence, in fact, no-clients of the translocon even by adding a SP are rejected (23-26)."
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Table 1-4 – If one wants to discuss isoforms, one should show alignments of both, RNA and primary protein structure. This should be done with sufficient resolution of the figure!

Decision letter (RSOB-19-0244.R0)

06-Jan-2020

Dear Dr Russo,

We are writing to inform you that the Editor has reached a decision on your manuscript RSOB-19-0244 entitled "Understanding the mammalian TRAP complex function(s)", submitted to Open Biology.

As you will see from the reviewers' comments below, there are a number of criticisms that prevent us from accepting your manuscript at this stage. The reviewers suggest, however, that a revised version could be acceptable, if you are able to address their concerns. If you think that you can deal satisfactorily with the reviewer's suggestions, we would be pleased to consider a revised manuscript.

The revision will be re-reviewed, where possible, by the original referees. As such, please submit the revised version of your manuscript within four weeks. If you do not think you will be able to meet this date please let us know immediately.

To revise your manuscript, log into https://mc.manuscriptcentral.com/rsob and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, please revise your manuscript and upload a new version through your Author Centre.

When submitting your revised manuscript, please respond to the comments made by the referee(s) and upload a file "Response to Referees" in "Section 6 - File Upload". You can use this to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the referee(s).

Please see our detailed instructions for revision requirements
https://royalsociety.org/journals/authors/author-guidelines/

Once again, thank you for submitting your manuscript to Open Biology, we look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Sincerely,
The Open Biology Team
mailto: openbiology@royalsociety.org

Reviewer(s)' Comments to Author(s):

Referee: 1

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Author's Response to Decision Letter for (RSOB-19-0244.R0)

See Appendix A.

RSOB-19-0244.R1 (Revision)

Review form: Reviewer 1

Recommendation
Major revision is needed (please make suggestions in comments)

Do you have any ethical concerns with this paper?
No

Comments to the Author
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1- Abstract. The first sentence is incorrect after the revision, since 1/3 of the proteins are not translocated or "reside" into the ER. Actually, this percentage of proteins are translocated or 'inserted' through the ER, but a large population can move to other membranes like Golgi, plasma,…, meaning that not all the membrane proteins inserted into the ER in fact "reside" in the ER.
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The sentence (line 9) "In mammalians,…" it's incorrect in its current form, several truncated forms of strict cotranslationally inserted proteins as short as 86-96 residues have been crosslinked to SRP and/or Sec61alpha. Examples: DOI:
10.1038/nsmb994 doi: 10.1128/JVI.00125-10.
The expression "no-clients of translocons…" in the last sentence of the introduction has no sense to me.
In general, the introduction of this review must be carefully curated, for that the author should read and cite some authorized recent revisions, like doi: 10.1146/annurev-biochem-013118-111717 and doi: 10.1515/hsz-2014-0205, to avoid incorrections or imprecise formulations related to the mechanisms of targeting and cotranslational insertion of membrane proteins.
3- Fig. 1. There is an extra loop between TM2 and TM3 in TRAP gamma that should be removed.
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Review form: Reviewer 2

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Here some examples:
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“These 3D imaging techniques allow the visualisation of complexes in their physiological environment associated with native membranes (10, 11) when the structure does not exceed a certain thickness (0.5–1 μm).” – the cited journals do not fit to the massage

“The open state can accommodate the unfolded chain and alpha-helix (13).” – please site an original paper, not a review

“TRAP is a ubiquitous protein complex present in all eukaryotes.” – Please cite the original data showing the presence of TRAP in yeast
“TRAP gamma is very close to the ribosomal protein rpl38 and an interaction between is plausible;” ???

Decision letter (RSOB-19-0244.R1)

13-Mar-2020

Dear Dr Russo,

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As you will see from the reviewers’ comments below, there are a number of criticisms that prevent us from accepting your manuscript at this stage. The reviewers suggest, however, that a revised version could be acceptable, if you are able to address their concerns. If you think that you can deal satisfactorily with the reviewer’s suggestions, we would be pleased to consider a revised manuscript.

The revision will be re-reviewed, where possible, by the original referees. As such, please submit the revised version of your manuscript within four weeks. If you do not think you will be able to meet this date please let us know immediately.

To revise your manuscript, log into https://mc.manuscriptcentral.com/rsob and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, please revise your manuscript and upload a new version through your Author Centre.

When submitting your revised manuscript, please respond to the comments made by the referee(s) and upload a file "Response to Referees" in "Section 6 - File Upload". You can use this to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the referee(s).

Please see our detailed instructions for revision requirements
https://royalsociety.org/journals/authors/author-guidelines/

Once again, thank you for submitting your manuscript to Open Biology, we look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Sincerely,
The Open Biology Team
mailto: openbiology@royalsociety.org

Editor's comments to Author:
Please address the comments of the referees and the quality of some of the images used will need improving.

Reviewer(s)' Comments to Author(s):

Referee: 1

Comments to the Author(s)
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Referee: 2

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"TRAP is a ubiquitous protein complex present in all eukaryotes." – Please cite the original data showing the presence of TRAP in yeast
"TRAP gamma is very close to the ribosomal protein rpl38 and an interaction between is plausible;" ???

Author's Response to Decision Letter for (RSOB-19-0244.R1)

See Appendix B.

Decision letter (RSOB-19-0244.R2)

23-Apr-2020

Dear Dr Russo

We are pleased to inform you that your manuscript entitled "Understanding the mammalian TRAP complex function(s)" has been accepted by the Editor for publication in Open Biology.

You can expect to receive a proof of your article from our Production office in due course, please check your spam filter if you do not receive it within the next 10 working days. Please let us know if you are likely to be away from e-mail contact during this time.

Thank you for your fine contribution. On behalf of the Editors of Open Biology, we look forward to your continued contributions to the journal.

Sincerely,
The Open Biology Team
mailto: openbiology@royalsociety.org

Appendix A

Referee 1

1, 2 – Sentences have been rephrased and language improved.
3 – The reference has been added (originally was UniProt but I found a publication).
4 – TRAM 1/ 2 has been removed, only TRAM is mentioned in all paper.
5 – This sentence is changed with the following: However, the mature protein plays also a role (29, 30); indeed, no-clients of translocons even by adding a SP are rejected (31-33). (last two lines of the Introduction). 6 - The yellow, green, and black (figure) is explained.
7 – Fig. 3: no data are present about TRAP subunits PBD structure; I used RaptorX for prediction and also I included the previous fig.3 which is important to understand how the complex is localized in the ER membrane.
8 – The Tab. Screenshots have been considerably improved and the program Geneious that I used is mentioned. The transmembrane domains are shown in all protein alignments and in the legend the different domains are s specified. Moreover, there is the figure 1 that shows these domains.
9 – In the paragraph is mentioned type I membrane protein (first sentence).
10 – Fig. 4, I added to the cartoon the rpl38 protein.
11 – I have written more general sentences because I cannot explain precisely what is the difference between TRAP and TRAM.
12 - The right reference has been written.
13 – The literature has been revisited.
14 - The figures have been removed. The STRING consortium is mentioned at the end of the paper (there is written about STRING prediction in the text), (also RaptorX).
15 – Tab. Corrected.
16 – This was a mistake I copied the text from another my document.
17 - Sec62 as well Sec63 are described in the introduction.
18 – Tab. 8 refers to last paragraph and it is mentioned.

Referee 2

Shortly I introduced the translocon of prokaryotes, the first sentences (reference 1).

All references have been revisited.

Sentences have been rephrased and language improved.

Some figures have been removed: 1, 6, 7. The tables considerable improved.

The molecular weight of TRAP has been corrected (about 90 Kda).

I added the alignment of RNA of the different isoforms. However, I did not find data about mRNA, what I show is retrotranslation from protein sequences. I do not know if it is worth to show these RNA alignments. (?)

Many thanks

Appendix B

Referee 1

1. Abstract: first sentence changed.
2. Introduction: revised all introduction, removed superfluous sentences and corrected some sentences. The sentence “no-clients of the translocon…” has been changed to explain that the sequence of the mature protein is also relevant for translocation.
3. Figure 1: extra loop removed.
4. Replaced beta -barrels with beta-sheets, actual page 15.
5. Reference removed and added the new reference.
6. Reference removed.
7. String introduced.
8. “Expression” is added.
9. “see below” is added.
10. I did not understand this point…and did not make chances.
11. Table (B, non-canonical EF-hand domain alignment) is cut, no extra lines.
12. Changed the verb with suggest.

Referee 2

Many superfluous sentences have been removed, probably it is a more focused review paper. Spelling corrected (I hope completely).

Citations corrected; figures improved.

References 10-11 removed and added the proper reference.

Reference 13 removed and added another reference.

TRAP reference that contains also data about yeast is specified.

TRAP gamma and rpl38 are very closed by cryo-EM data, but the sentence “an interaction between them is plausible” has been removed.

Thank you very much for your very constructive reviews.