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The extraordinary energy metabolism of the bloodstream Trypanosoma brucei forms: a critical review and hypothesis

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Reviewer 1: Hassan Hashimi

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Manuscript reviewed 2022-07-28: *Only major points included.*

Reviewer 1

In the first full paragraph on page 6, the authors write: "From the functional side, the fundamental mitochondrial processes are drastically altered in trypanosomatid life forms…". First of all, 'trypanosomatids' alone suffices at end of quote. Second and more importantly, this is a very ambiguous statement. Do the authors mean that mito metabolism is different in different trypanodomatids? If yes, then the authors should also cite Škodová-Sveráková et al., 2014 Mol. Microbiol. 96: 55-67. If they mean that these processes are remodeled to cater to different life cycle stages, then they should replace trypanosomatids with 'Trypanosoma' as they only discuss T. cruzi and T. brucei in this part. In any case, the authros should clarify what they mean in this paragraph.

Authors

We thank the reviewer for the observations. We have corrected this sentence to stress that mitochondrial function is altered throughout the trypanosomatid life-cycle, regardless of the species, as following:

"From the functional side, the fundamental mitochondrial processes are drastically altered along trypanosomatids life-cycle, including the activities of tricarboxylic acid (TCA) cycle…"

Reviewer 1

On the same page they write: "Noteworthy is the fact that the inability of BSF to perform OXPHOS is not due to the absence of ETS, but to a remarkable remodeling of its function. Indeed, ETS in BSF is essentially carried out by a reduced form of electron transfer…". On page 7 they ten write: "Given the non-conservative nature of respiration in BSF, these parasites indeed maintain $\Delta\Psi_m$, not by the activity of the ETS complexes…" These two quotes are to illustrate the ambiguity of the authors usage of 'ETS'. Yes, electron transport chains are a common feature in life, from photosynthesis to cellular respiration to GSPh discussed here. But this is also used to describe complexes I-IV in the canonical respiratory chain. I think it is important that the authors make a distinction between the two concepts as not to cause confusion to the readers.

Authors

The definition of an electron transport system is any protein complex in which the redox potential of their components drives the electron transfer from a reduced donor to a less reduced acceptor. This is true for any electron transport system, including photosynthesis, cytochrome-dependent and independent respiration. The latter is the case for BSF electron transfer as the ETS is not mediated by cythchorme-dependent complexes but rather to glycerolphosphate dehydrogenase and alternative oxidase, only. Indeed, electron transport systems are also defined even for non mitochondrial electron transport such as the NADPH oxidase complex that is assembled at the plasma membrane of many eukaroytic cells. Therefore, we maintained the definition of the BSF respiration understanding that it represents a reduced form of a classical electron transport system.

Reviewer 1

The third paragraph on page 7 discusses PCD in trypanosomatids, a relevant topic given the model they propose at the end of the manuscript (e.g. Fig. 3). I understand that the authors or proponents for the existence of PCD in trypanosomatids and I respect their opinion. However, I am of the opinion that this phenomenon, that there is a truly programmed process requiring expression of specific genes or stabilization/modification of gene products to mediate defined death pathways, still has not been definitely demonstrated. For example, the classical apoptotic (not PCD as they write) cell markers that have been observed are due to a cell death signaling pathway, and thus can be either caused or the cause of cell death. Thus, I disagree that these are "sufficient evidence" to support the existence of cell death. I am not asking the authors to change their stance unicellular PCD, but simply acknowledge that effectors of PCD have still not been identified, making the existence of unicellular PCD a still unverified and debated hypothesis. They can of course mention the observation of markers to support this hypothesis, but clarify these are not definitive proof. Anyway, I do not see any reason for PCD to be invoked in their final model: it is clear the maintenance of PMF is essential for BSF (for reason mentioned on full paragraph 3 on page 12) and thus its maintenance is essential for survival, not necessarily to inhibit PCD.

Authors

We agree with the reviewer´s point of view regarding the controversies on the trypanosomatids cell death processes. Indeed, we have considered this issue at the last paragraph of page 7, where we pondered that it is still debatable and an open discussion. In order to acknowledge the reviewer´s comments, we then changed all "programmed cell death" statements to just "cell death" along the manuscript

Reviewer 1

Two more minor points on the paragraph mentioned in the above point. 1) Please do not use the term 'higher eukaryotes'. This implies a directionality to evolution. They can replace this with 'animals' or 'metazoans'. If the authors mean plants too, while there is PCD in this lineage, this is most likely not via the classical intrinsic apoptosis pathways (see Dickman et al., 2017 Nat. Plants 3: 773-779.). 2) PS should be written 'phosphatidylserine'.

Authors

We thank the reviewer for this comment and we have changed all statements of "higher eukaryotes" to " animals" and "phosphatidylserine" instead of "PS" throughout the revised manuscript.

Reviewer 1

The second full paragraph on page 10 discusses the phylogeny of AOX and cites Luévano-Martínez et al 2020. The AOX phylogenetic tree presented there is not very convincing for many reasons. Please cite instead Pennisi et al., 2016 J Mol Evol 82: 207-18 instead, which better supports the claim made here.

Authors

We have added the suggested reference at the stated paragraph at page 10.