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Mitochondrial plasticity in trypanosomatids as a stress adaptation mechanism

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Reviewer 1: Marcus Oliveira
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Manuscript reviewed 2022-09-09: *Only major points included.*

Reviewer 1

The work of Bombaca and colleagues revises the knowledge on Trypanosomatid mitochondrial structure and physiology generated by their laboratory over the years with a focus on the use of parasite mitochondrial processes as potential anti-trypanosomal targets. The research group of Dr. Menna-Barreto has an extensive experience in these topics and the manuscript is in general well-written. I have observed some issues that authors should consider useful to improve the manuscript before formal acceptance as follows.

While the discussion of the results produced by their own group is welcomed, I think the authors should expand the coverage of the knowledge about mitochondria in trypanosomatids by including the contribution from other important groups over space and time. For example, the authors did not discuss the importance of proline and fatty acid metabolism to T. cruzi (https://pubmed.ncbi.nlm.nih.gov/34661234/; https://pubmed.ncbi.nlm.nih.gov/23894476/; https://pubmed.ncbi.nlm.nih.gov/25623067/; https://pubmed.ncbi.nlm.nih.gov/32315030/; https://pubmed.ncbi.nlm.nih.gov/33819309/; https://pubmed.ncbi.nlm.nih.gov/24587468/). In the same line, the key discoveries of mitochondrial calcium and pyruvate metabolism from DoCampo, Radi and Vercesi laboratories should also be included and properly discussed (https://pubmed.ncbi.nlm.nih.gov/2500059/; https://pubmed.ncbi.nlm.nih.gov/33824204/; https://pubmed.ncbi.nlm.nih.gov/19053945/; https://pubmed.ncbi.nlm.nih.gov/28487431/; https://pubmed.ncbi.nlm.nih.gov/31064825/; https://pubmed.ncbi.nlm.nih.gov/32184243/; https://pubmed.ncbi.nlm.nih.gov/32947181/; https://pubmed.ncbi.nlm.nih.gov/34085343/). This reviewer emphasizes that the above references are just some of the examples of the body of knowledge that authors missed to include and discuss and which should be expanded to provide a broader and comprehensive picture of mitochondrial metabolism in trypanosomatids, beyond those generated by their laboratory.

Authors

Thanks for the comments. In the invitation, the suggested length of the manuscript was small; then, we opted to review our contribution to the field in last decades, well focused on the scientists of our field. Before answer these queries, we contacted the editors (Dr. Vito de Pinto and MSc. Lisa Tindle-Solomon) to understand the journal position in relation to the length. The answer was "We realize that since the time of the authors' submission the strategy went from a print collection to a strictly online volume, removing the limit on length. Our suggestion would be to continue with the short review to publish now and then create a living communication whereby the authors take the additional 2-3 months to create a full review which addresses the literature gaps mentioned by the reviewers, which would then be submitted as a second edition (version) of the manuscript." For sure, we agree with the reviewer, and we intend to add, in the second manuscript version, topics related to trypanosomatids' antioxidant system (trypanothione metabolism and others antioxidant players), carbohydrate and fatty acid metabolisms, and pyruvate metabolism. We will focus in metabolic adaptations described to *T. cruzi*, *Leishmania* spp., monoxenous trypanosomatids (*Strigomonas culicis* and others) and, as highlighted by the reviewer, *T. brucei*; thus, we believe that the readers will have a good overview about bioenergetic and mitochondrial metabolism of trypanosomatids. At the moment, we corrected the points specified by the reviewer in the questions below, adding some important information about mitochondrial metabolism of *T. cruzi*, *Leishmania* spp. and *T. brucei* in the topic "*background*".

Reviewer 1

Considering the manuscript is a review paper, I have noticed the complete absence of a discussion about the remarkable features of the Trypanosoma brucei mitochondria. In this regard, the knowledge of unique mitochondrial processes in T. brucei (AOX and reversed ATP synthase) in bloodstream mitochondria are critical ones to be discussed and explored.

Authors

Thanks for the comments. An update about trypanosome alternative oxidase was included, as well as, important aspects of *T. brucei* mitochondrial functionality were also added. We believe that the second manuscript version will provide a more complete overview about energy substrates (especially carbohydrates) used by each parasite form and its availability in the host.

Reviewer 1

A critical aspect is the true novelty of the present manuscript considering that the authors published another review on the very same topic last February (https://pubmed.ncbi.nlm.nih.gov/35195164/). In my opinion, the authors should clearly explain the novel aspects that the present manuscript brings to the discussion beyond those already covered in the previous review to avoid overlapping.

Authors

The reviewer raised a very important point nowadays. Our review in MIOC intitled *"Is the mitochondrion a promising drug target in trypanosomatids?"* was really focused on the trypanosomatids' mitochondria as a target of drugs; in that opportunity, we also

pointed the mitochondrial import system as a promising target in these parasites due to the differences in comparison to the mammalian host system. This review was proposed in a special issue in a context of the creation of Brazilian Multicentre Working Group in Molecular Mechanisms of Action of Trypanocidal and Leishmanicidal Drugs focusing on novel chemotherapeutic strategies. Here, in BEC manuscript, we were not restricted to chemotherapic aspects; we included our contribution in untreated parasites: (a) mitochondrial comparative studies among Leishmania spp. and also the effect of nitric oxide resistance; (b) mitochondrial remodeling during *T. cruzi* differentiation and the effects of stress conditions in its mitochondrial function; (c) analysis of mitochondrial metabolism of monoxenous parasite *S. culicis*, our important model, whereas we are studying different metabolic and biochemical aspects. None of this information was included in MIOC review. For sure, once we also work with chemotherapy, and it is a crucial point to be debated (as mitochondrial damage is one of the most commonly described effects in trypanosomatid chemotherapy studies), we also shortly described our main findings about the effect of some drugs in trypanosomatids' mitochondria over BEC manuscript. In addition, anything about the potential of import system, described in MIOC manuscript, was mentioned here and all the figures were different, with unpublished images.