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

Authors: Alencar MB, Ramos EV, Silber AM, Zíková A, Oliveira MF

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Reviewer 3: Carlos Robello

Institut Pasteur de Montevideo and Facultad de Medicina, UDELAR, Uruguay

Manuscript reviewed 2022-10-02: *Only major points included.*

Reviewer 3

In this work, the authors make an exhaustive and entertaining review of the intermediary metabolism of the blood form of *Trypanosoma brucei*, the causative agent of sleeping sickness or African trypanosomiasis.

During infection in mammals, these parasites present very particular characteristics, among which the authors highlight the almost null mitochondrial activity, the glycerol 3 P shunt, the TAO alternative oxidase, and the reversal of the ATP synthesis reaction by the complex V, which implies a unique case in nature. In addition to conducting an exhaustive review, the authors suggest how TAO activity constitutes a defense mechanism against oxidative stress and the relevance of complex V in maintaining the proton gradient. They also review the dialogue between glycosomes and mitochondria, and the relevance of glycolysis as a source of energy for ATP hydrolysis.

In fact, a hypothesis is proposed as to how the GSh-TAO system constitutes a complementary antioxidant defense system in BSF.

In short, this is an excellent review that provides novel elements to explain this original metabolic mechanism.