Transport of pyruvate into the mitochondrion of Trypanosoma brucei

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Trypanosoma brucei is a pathogen of livestock and humans transmitted by tse-tse flies in sub-Saharan Africa. Different life-cycle stages of trypanosomes present adaptations to their specific environment. In bloodstream and procyclic T. brucei, these include changes to mitochondrial morphology and function, and overall metabolic rearrangements reflected by different spectra of metabolic end products. In bloodstream T. brucei, ATP is generated primarily by glycolysis, pyruvate being the predominant excreted product of metabolism. In contrast, procyclic-stage T. brucei, found in the midgut of the insect vector where glucose is scarce, depend on mitochondrial catabolic pathways for ATP production. Proline and threonine are candidate carbon sources for these stages. In trophozoites, these are eventually metabolized to succinate, acetate and glycine. Regulating the availability of pyruvate in the mitochondrion is one of the modes of balancing oxidative phosphorylation and glycolysis; in bloodstream T. brucei this balance is shifted heavily towards glycolysis. We seek to determine whether T. brucei transports pyruvate into the mitochondrion using a mitochondrial pyruvate carrier homologous to the one recently identified in fruit fly, human and yeast cells (MPC). In addition, we address the relative importance of the pyruvate transporter in procyclic and bloodstream trypanosomes. To this end, we identified two MPC homologs in the genome T. brucei and confirmed the mitochondrial localization of the epitope-tagged proteins in both procyclic and bloodstream stages. We generated MPC1 knock-out cell lines in both these stages, showing that the pyruvate transporter is dispensable for T. brucei under standard culture conditions. The adaptations of mitochondrial metabolism in this model, as documented by end product analysis using HPLC and NMR, let us comment on mitochondrial metabolism in T. brucei in general.

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The critical role of Na+/Ca2+ exchanger on the maintenance of T-tubule structure

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Cardiac Na+/Ca2+ exchanger (NCX1) is the primary Ca2+ extrusion system in beating myocytes, essential for Ca2+ homeostasis, and important in Ca2+ handling during excitation–contraction (E–C) coupling. NCX1 is specially localized in T-tubule and can be close to dyad, where is a predominantly E–C coupling take place. Therefore, T-tubule disorganization is linked to decreased contractility in heart failure (HF). Despite of T-tubule remodeling be correlated with Ca2+ handling defects in failing hearts (FH), the molecular mechanism has remained unclear. To examine whether the alteration of NCX1 expression and activity relate to the disorganization of T-tubule structure in FHs, we generated novel transgenic mice expressing NCX1 cardiac-specifically and inducibly, and examined the effect of inducing NCX1 expression during the progression of HF. We followed changes in NCX1 activity and expression during HF progression over 16 weeks in these mice, after transverse aortic constriction (TAC)-surgery. In TAC hearts, NCX1 activity increased over the first few weeks, but started to drop from 8 weeks after TAC before the onset of T-tubule disorganization and myocyte contractile dysfunction, which are common features in failing myocytes. Over the progression of HF, the expression of junctophilin-2 located at T-tubule/sarcoplasmic reticulum (SR) junction was gradually reduced in TAC hearts. Inducing NCX1 expression