Abstract

Mitochondria perform various important functions in cells. They are the main site of energy metabolism, biosynthetic and regulatory processes, and the center of iron metabolism. Additionally, mitochondria are also the central organelle responsible for the production of potentially dangerous reactive oxygen species and possess a self-destructive arsenal capable of inducing whole-cell apoptosis. This single organelle thus controls the fate of the entire cell. Given these facts, this organelle has become the focus of interest for many scientists and pharmaceutical companies developing drugs targeting mitochondria. During evolution, unicellular parasites have evolved several mechanisms to survive, defend themselves and reproduce in the hostile environment of their host. One of these mechanisms is the ability to adapt its mitochondrial metabolism to maintain the viability of the whole cell.

This work focuses on mitochondria from two different perspectives:

First, concerning the phenomenon of nutritional immunity, we studied the effect of iron and copper deprivation on the mitochondria of the "brain-eating" amoeba *Naegleria fowleri.* Proteomic analysis of cells pre-incubated with specific chelators, together with the determination of several enzyme activities and measurements of oxygen consumption, revealed that *N. fowleri* mitochondria adapt to these limiting factors by upregulating alternative components of the branched electron transport chain (ETC) to compensate for lower activity of other components in ETC. Moreover, in the case of iron deprivation, we demonstrated an interesting trend of downregulation of iron-dependent cytosolic enzymes in an attempt to spare iron to maintain a vital pathway of energy metabolism, the ETC.

Second, we elucidated the mode of action of the mitochondrially targeted anti-cancer drug MitoTam on the bloodstream form of *Trypanosoma brucei*. The mode of action in cancer cells is often associated with the activity of complex I, which is rather dispensable in the bloodstream form of *T. brucei*. Functional analysis showed a rapid effect of MitoTam on mitochondrial processes, manifested by reduction of cellular respiration, lowering of ATP levels, rapid dissipation of mitochondrial membrane potential, and also disruption of mitochondrial integrity leading to cell death. Altogether, we have identified another potential candidate drug to combat sleeping sickness and confirmed that drug repurposing is a powerful tool for finding new therapeutic options for neglected diseases.