# An atypical mitochondrial carrier that mediates drug action in Trypanosoma brucei

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Elucidating the mechanism of action of trypanocidal compounds is an important step in the development of more efficient drugs against Trypanosoma brucei. In a screening approach using an RNAi library in T. brucei bloodstream forms, we identified a member of the mitochondrial carrier family, TbMCP14, as a prime candidate mediating the action of a group of anti-parasitic choline analogs. Depletion of TbMCP14 by inducible RNAi in both bloodstream and procyclic forms increased resistance of parasites towards the compounds by 7-fold and 3-fold, respectively, compared to uninduced cells. In addition, down-regulation of TbMCP14 protected bloodstream form mitochondria from a drug-induced decrease in mitochondrial membrane potential. Conversely, over-expression of the carrier in procyclic forms increased parasite susceptibility more than 13-fold. Metabolomic analyses of parasites over-expressing TbMCP14 showed increased levels of the proline metabolite, pyrroline-5-carboxylate, suggesting a possible involvement of TbMCP14 in energy production. The generation of TbMCP14 knock-out parasites showed that the carrier is not essential for survival of T. brucei bloodstream forms, but reduced parasite proliferation under standard culture conditions. In contrast, depletion of TbMCP14 in procyclic forms resulted in growth arrest, followed by parasite death. The time point at which parasite proliferation stopped was dependent on the major energy source, i.e. glucose versus proline, in the culture medium. Together with our findings that proline-dependent ATP production in crude mitochondria from TbMCP14-depleted trypanosomes was reduced compared to control mitochondria, the study demonstrates that TbMCP14 is involved in energy production in T. brucei. Since TbMCP14 belongs to a trypanosomatid-specific clade of mitochondrial carrier family proteins showing very poor similarity to mitochondrial carriers of mammals, it may represent an interesting target for drug action or targeting
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