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Plasmodium falciparum: Functional mitochondrial ADP/ATP transporter in *Escherichia coli* plasmic membrane as a tool for selective drug screening

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Abstract

Plasmodium falciparum mitochondrial ADP/ATP transporter or adenylate translocase (PfAdT) was previously characterised at the molecular level and intracellularly located by immuno-electromicroscopy. Inhibition of this transporter blocks parasite development in erythrocytes. In this study, PfAdT was expressed in C43 (DE3) *Escherichia coli* strain under isopropyl beta-D-thiogalacto-pyranoside (IPTG) induction to screen inhibitory molecules. PfAdT was integrated directly into the bacterial cytoplasmic membrane. Whereas IPTG-induced bacterial cells imported radioactively labelled ATP, non-induced cells did not. The transporter bound specifically ADP and ATP, but not AMP. IPTG-induced cells preloaded with labelled ATP exported ATP after exogenous addition of unlabelled ADP or ATP, indicating a counter exchange transport mechanism. Bongrekic acid and atractyloside, two well-known specific inhibitors of mitochondrial ADP/ATP transporter, were tested. This experimental model was evaluated using three Malagasy crude plants extracts which have shown antiplasmodial activity on *in vitro* parasite cultures.

Index Descriptors and Abbreviations: Malaria, *Plasmodium falciparum*; *Rickettsia prowazekii*; *Arabidopsis thaliana*; *Brachylaena ramiflora*; *Phyllarthron bernierianum*; *Strychnos* sp.; C43 (DE3) *E. coli*; Natural plant extracts; ADP/ATP carrier; Bongkrekic acid; Plants extracts; ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; ATR, atractyloside; BA, bongkrekic acid; EDTA, ethylene diamine tetraacetate; IPTG, isopropyl beta-D-thiogalacto-pyranoside; PfAdT, *P. falciparum* adenylate translocase or ADP/ATP transporter; PB, phosphate buffer; SDS, sodium dodecyl sulphate; YT, yeast tryptone

1. Introduction

Malaria is still the most serious and prevalent cause of morbidity and mortality in tropical and sub-tropical countries, constituting a major health problem for individuals and communities and impairing economic development. At present, at least 300 million people are affected by malaria and about 1.5 million people die each year from this disease. Pregnant women and children are especially vulnerable to the disease and one child in 20 is killed by it before the age of five. Of the four species specific for humans *Plasmodium falciparum* is the most virulent one, developing drug resistance in many parts of the world and continuing to spread. To overcome this drug resistance, new preventive and curative antimalarial molecules need to be synthesised and new molecular therapeutic targets characterised.

Although *P. falciparum* is considered a homolactate fermentor and possesses an acristate mitochondrion, parasite mitochondrion plays an important role in ATP production (Ginsburg et al., 1986; Van Dooren et al., 2006). Initially, it was suggested that *Plasmodium,* like typhus *Rickettsia*, another obligate intracellular parasite (Winkler, 1976) may utilise an ADP/ATP exchange system to facilitate

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