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Investigation of the role of ABC proteins in the resistance to paromomycin in Leishmania amazonensis

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Abstract
Leishmaniasis is a parasitic disease with wide geographic distribution in tropical and subtropical areas, including Brazil where an increased number of cases in urban areas has been reported in the recent years. No vaccines are available for control of the disease and chemotherapy is restricted to some drugs like antimony and amphotericin B. Although not yet approved for the treatment of leishmaniasis in Brazil, paromomycin has been used in the treatment of visceral leishmaniasis in Southeast Asia with effectiveness of approximately 90%. To understand the mechanism of action and resistance of this drug in Leishmania, we aim to investigate the role of a subfamily of ABC (ATP binding cassette) proteins in the mechanisms of paromomycin resistance by gene transfection and overexpression of these genes in Leishmania amazonensis.

Key words: *Leishmania amazonensis, paromomycin, drug resistance*

Introduction

Leishmaniasis is a parasitic disease with wide geographic distribution in Brazil with an increased number of cases in urban areas in recent years. Although not yet approved for the treatment of leishmaniasis in Brazil, paromomycin has been already used in the treatment of visceral leishmaniasis in Southeast Asia. In *Saccharomyces cerevisiae*, the elongation factor 3 (EF-3) is related to translation machinery and increased levels of this protein in yeast affects the susceptibility to paromomycin[1]. Search for homologs in *Leishmania mexicana* genome databases indicated that EF-3 has similarity to members of a subfamily ABC (ATP binding cassette) proteins. In this work, we aim to investigate the role of this subfamily of ABC proteins in the mechanisms of paromomycin resistance by gene transfection and overexpression of these genes in *Leishmania amazonensis*, a endemic species responsible for cutaneous and diffuse cutaneous leishmaniasis in Brazil.

Results and Discussion

We first searched for homologs of EF-3 in *Leishmania* and *C. elegans* genome databases. BLAST analyzes indicated some similarity (approximately 15%) to members of the subfamily F of ABC proteins of *C. elegans* and *Leishmania*. Three copies of these genes are present in the genome of the main species responsible for the leishmaniasis. In the genome of *L. mexicana*, the most closed related species to *L. amazonensis*, these genes are located in the chromosomes 3, 19 and 32. To investigate the role of these ABC proteins in paromomycin susceptibility and resistance, these genes were amplified (Fig. 1), and then will be cloned, transfected and overexpressed in *L. amazonensis* as described [2]. Transfectants overexpressing each one of these genes will be then evaluated by paromomycin susceptibility essays.

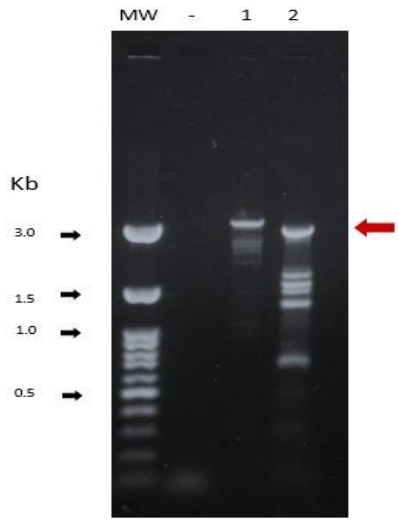

Figure 1. Amplification of LmxM.03.0160 and LmxM.19.0800 genes by PCR using primers directed to the intergenic regions of these genes of *L. amazonensis*. Legend: 1- LmxM 3.160 gene (≈ 3,0 kb), 2- LmxM 19.800 gene (≈ 3,0 kb).

Conclusions

This study will contribute to understand the mechanism of action and resistance to paromomycin in *Leishmania* and investigate whether these ABC proteins are involved or not in paromomycin susceptibility and resistance in leishmaniasis.

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1 Sandbaken, M.G., et al.. *J Biol Chem*, **1990**. 265, 15838.

2 El Fadili, K., et al. *Antimicrob Agents Chemother*, **2005**. 49, 1988.