Mini Review

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2019.21.003555

Antimony Resistance in *Leishmania* Parasites may be Related to an Increased Virulence

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ARTICLE INFO

Received: August 27, 2019

Published: September 04, 2019

Citation: Laísa Vilar Cordeiro, Francisco Patricio de Andrade Júnior, Edeltrudes de Oliveira Lima. Antimony Resistance in *Leishmania* Parasites may be Related to an Increased Virulence. Biomed J Sci & Tech Res 21(1)-2019. BJSTR. MS.ID.003555.

ABSTRACT

Chemotherapy is the main approach for leishmaniasis management, and antimonial (Meglumine antimoniate and Sodium stibogluconate) are the first class of drugs applied to leishmaniasis treatment. Treatment with these drugs has several limitations, including the progressive emergence of resistant parasites. Aggravating this situation, recent evidence that the antimonial resistance and virulence may be correlated in *Leishmania* sp. have been published in the literature, and this may contribute to the severity of the disease, directly reflecting on the prognosis of infected patients. The correlation between *Leishmania* virulence and antimony resistance parameters is not fully understood yet, but due to its clinical relevance, it is critically necessary further enlighten this fact.

Introduction

The leishmaniasis are complex heterogenic vector-borne diseases caused by *Leishmania* spp. (Protozoa, Kinetoplastida, Trypanosomatidae) and spread by female sand flies [1]. Chemotherapy is the main approach for leishmaniasis management. However, the combined problems of parenteral administration and anti-leishmaniasis substantial side effects are factors that hinder treatment. In addition, the selection of resistant parasites carrying genetic mutations that lessen the parasite's response to drugs may emerge upon mass drug administration [2]. There are only a few drugs available for leishmaniasis treatment and most of them have been in use for quite some time. Pentavalent antimonial, amphotericin B, pentamidine, miltefosine and paromomycin constitute the resources available for leishmaniasis chemotherapy [3]. Antimonial (Meglumine antimoniate and Sodium stibogluconate) are the first class of drugs applied to leishmaniasis treatment. These toxic compounds have a narrow therapeutic window but are still in use in various regions of the world such as Latin America and East Africa [2,3].

Another complicating factor includes the fact that *Leishmania* parasites present the possibility of suffering considerable genomic changes, such as chromosomal aneuploidies, and changes in gene expression pattern, which appear to be involved in the adaptation of these organisms to the presence of the drug. Over the last 10 to 20 years, there has been an increased in clinical resistance to antimonial, which has even led to the abolition of use in some regions, for example, in North Bihar in India [2]. Some studies on prokaryotes and eukaryotes show that drug resistance is usually related to a reduction in the fitness of microorganisms, since there is a decrease in growth, virulence and transmissibility between hosts [4,5]. However, it has recently been observed that some species of *Leishmania*, especially *L. donovani*, resistant to antimonial appear to have developed a series of molecular adaptations that lead to an increased parasite fitness even in the absence of the drug. This ability has been related to the competence to generate metacyclic forms, which have greater power of host infection. The plastic nature of the genome of these parasites makes them highly

adaptable, being able to modulate gene expression through gene amplification or deletion and alter chromosomal ploidy in response to drug-stress [6-9].

Antimony Resistance and Increased Virulence

Vanaerschot and collaborators [6] analyzed antimonial susceptible and resistant clinical isolates of *L. donovani*. The authors observed that resistant parasites showed lower sensitivity to oxidative and Nitrosative stress *in vitro*. The *in vitro* macrophage infection rate was significantly higher in drug-resistant strains and they were also more infective *in vivo*, reaching a higher parasitic load in both spleen and liver of infected Balb/c mice. The authors suggest that higher stress resistance and a greater number of metacyclic forms may contribute to resistant strains had superior survival skills as promastigotes and as amastigotes compared to the sensitive's strains. Ouakad and colleagues [7] demonstrated that antimony-resistant *L. donovani* strains had twice as many metacyclic forms as those found in antimony-sensitive cultures. Resistant cultures also had higher infection capacity in murine macrophages and were more resistant to complement-mediated lysis. Another study also analyzed antimony-resistant *L. donovani* strains found higher *in vivo* infection power [8]. Another research, by Moura and colleagues [9], used *L. infantum* strains isolated from refractory patients to antimony treatment (relapse cases) and responsive patients (control group). Macrophage infection was higher with *L. infantum* isolates from relapse cases and correlated with enhanced interleukin 1-β production, furthermore, these parasites stimulated inflammatory cytokines and were resistant to macrophage killing mechanisms, factors that may contribute to disease severity.

Conclusion

Findings between the possible correlation of increased virulence in antimonial-resistant *Leishmania* parasites raise a fundamental question about potential risks of selecting more virulent pathogens through massive chemotherapy interventions. Further work is needed to further clarify this fact and to lead to better guidelines for the treatment of these disorders.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2019.21.003555

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