EDITORIAL

Parasite, vectors and reservoirs as determinants of tegumentary leishmaniasis

Parasita, vetores e reservatórios como determinantes de leishmaniose tegumentar

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Tegumentary leishmaniasis is a concerning issue faced by public health systems in tropical and subtropical countries worldwide. While autochthonous cases of tegumentary leishmaniasis have been documented in all Brazilian states, the prevalence of tegumentary leishmaniasis is higher in the north and northeastern regions, which account for more than 70% of the cases in Brazil. In Brazil, *Leishmania* from different species can cause disease, but *Leishmania (Viannia) braziliensis* is the main causal agent of tegumentary leishmaniasis. *Leishmania (V.) braziliensis* can also cause different clinical forms of the disease such as cutaneous, mucosal, and disseminated leishmaniasis. Moreover, up to 18% of individuals living in an area of *L. (V.) braziliensis* transmission have evidence of infection but do not develop the disease[1]. Advances in the epidemiology, taxonomy, pathogenesis, immunology, and diagnosis of tegumentary leishmaniasis have been achieved in the last 20 years. However, additional studies are still needed in order to adapt these advances to clinical medicine to ameliorate the suffering of leishmaniasis patients. Moreover, very little is known about the development or identification of new drugs for leishmaniasis therapy. In the beginning of the last century, antimony was used to treat leishmaniasis and has been the therapy of choice for tegumentary leishmaniasis in Brazil ever since.

In their review, Brito et al. emphasize the diversity among *Leishmania* species, which are a large number of phlebotomine species with the ability to transmit leishmania, and reservoir hosts of the parasites[2]. Among the biological sciences, the greatest advances related to leishmaniasis in recent years have been in the field of immunology. There is no doubt that host immunological responses play a pivotal role in the pathogenesis of the disease and diversity of the clinical forms of tegumentary leishmaniasis. The finding that the Th1 type of immune response, which is characterized by the production of high levels of IFN-γ (the main cytokine involved in microphage activation), is associated with pathology rather than protection has led to the understanding of the pathogenesis of *L. braziliensis* infection[3,4]. These studies have not only increased our knowledge of how the infection progresses toward disease, but also have implications in therapy for leishmaniasis and vaccine development. However, it is clear that host immune response alone is unlikely to help elucidate how a single genus is able to cause such a heterogeneous group of diseases.

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Phone: 55 71 3237-7353
Received in 01/08/2012
Accepted in 06/08/2012

Recent epidemiologic, biochemical, and molecular biology studies indicate that *L.(V.) braziliensis* is polymorphic[5,6]. Moreover, there is an association between intra-species differences in *L. (V.) braziliensis* and clinical forms of tegumentary leishmaniasis[7]. Isolates of the same species of leishmania play a role in the therapeutic response to antimony. Drug-resistant strains among different *Leishmania* species have been reported, suggesting that the parasites are capable of adapting to drug pressure. Susceptibility to antimony varies among species and even between geographically distant strains of *L. (V.) braziliensis*. There is also evidence that *L. (V.) braziliensis* isolates may have susceptibility or resistance to nitric oxide; isolates resistant to nitric oxide *in vitro* have been derived from human cases in which antimony therapy failed[8]. Reports also indicate that parasite resistance to hydrogen peroxide may play a role in more severe forms of leishmaniasis. *Leishmania guyanensis* isolates capable of metastasizing in hamsters possess cytoplasmic peroxiredoxin and peroxidase activities different from those of non-metastatic parasites[9]. Moreover, *L. guyanensis* with a metastatic phenotype has isoforms of tryparedoxin peroxidase and elongation factor 1 beta different from those of non-metastatic strains. These studies show that intra-species differences of leishmania are associated with clinical forms of the disease as well as response to therapy. Knowledge about genotypic differences may also affect the diagnosis of leishmaniasis. For instance, the initial form of tegumentary leishmaniasis caused by *L. (V.) braziliensis* is cutaneous leishmaniasis. Patients with cutaneous lesions will develop mucosal or disseminated leishmaniasis only after days or weeks. Mucosal leishmaniasis requires higher doses of antimony to cure it. Meanwhile, disseminated leishmaniasis responds poorly to antimony therapy; in such cases, amphotericin B is the drug of choice. Advances in molecular biology are expected to make it possible to determine whether a strain is associated with a risk for the development of mucosal or disseminated leishmaniasis on the basis of the genotypic characteristics of the isolate.

The number of studies showing a role of the vector in the epidemiology and pathogenesis of leishmania infections has grown exponentially in the last 10 years. A great variety of phlebotomine sandfly vectors have been documented in Brazil, and a large proportion of them are exposed to *Leishmania* spp. infection. *Lutzomyia whitmany* and *Lutzomyia intermedia* are the most important vectors of *L.(V.) braziliensis* in Brazil. The salivary glands of phlebotomines have biochemical and immunological properties. Initial studies showing that administering the salivary glands of *L. longipalps* with *Leishmania major* increased parasite growth and pathology and prompted many subsequent studies; these studies indicate that not only do the salivary glands of sandflies play a role in the pathogenesis of leishmaniasis, but also that these salivary gland proteins are targets for vaccines against leishmaniasis. It is important

to note that the ability of salivary gland proteins to modulate immunological responses varies by *Lutzomyia* species. For instance, while immunological responses against salivary gland proteins of *L. longipalps* and *Phlebotomus papatasi* are associated with protection against leishmaniasis, evidence of an immune response against the *L. intermedia* salivary gland proteins is associated with the development of cutaneous leishmaniasis[10].

Progress in the identification of wild and synanthropic reservoirs of *L. (V.) braziliensis* has occurred in recent years. However, in a review published in this volume of the Journal of the Brazilian Society of Tropical Medicine[2], Brito et al. report that isolates from such animals need to be identified and characterized properly. A large number of small mammals have been documented as possible *L. (V.) braziliensis* reservoirs. However, further studies are necessary not only to determine the importance of these animals in the maintenance of the parasite but also to ascertain their roles in human transmission. Both the number of cases of leishmaniasis and areas of *L. braziliensis* transmission have increased in Brazil. Furthermore, both reservoirs and vectors play major roles in the expansion of the transmission areas of *Leishmania* spp. as well as the increasing occurrence of leishmaniasis cases in children and women.

CONFLICT OF INTEREST

The author declare that there is no conflict of interest.

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