Leishmaniasis control strategies

A critical evaluation of IDRC-supported research
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Leishmaniasis control strategies
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"Immunological Considerations in the Control of Leishmaniasis"

Immunological Considerations in the Control of American Tegumentary Leishmaniasis caused by Leishmania of the subgenus Viannia

By N.G. Saravia

1. Does natural infection confer resistance to new infection and disease? Are individuals who have had and recovered from leishmaniasis likely to experience leishmaniasis again?

The frequent presence of scars typical of prior leishmaniasis in patients consulting for the diagnosis and treatment of active lesions and the documentation of recurrent lesions due to the same of distinct parasites in prospectively evaluated patients, indicate that natural infection with Leishmania of the subgenus Viannia does not necessarily confer resistance. In fact, longitudinal assessment of the Pacific Coast of Colombia, indicated that individuals with evidence of prior leishmaniasis had a higher relative risk of new disease than did naive individuals. Continual exposure to infection and other factors associated with living in an endemic area may contribute to this pattern of recurrent disease. To our knowledge, recurrence is rare among individuals who have acquired leishmaniasis during temporary exposure to transmission, i.e. soldiers, laboratory workers. Requirements for immunoprophylaxis may therefore differ for individuals permanently residing in endemic areas and for those transitorily exposed.

2. Does infection with a particular Leishmania induce cross-protection to other Leishmania?

Considerable heterogeneity has been observed among Leishmania of the Viannia subgenus. Variation is phenotypic as well as genotypic, and evidence for antigenic heterogeneity has been provided by typing analyses utilizing monoclonal antibodies. Since experimental animals vary in their susceptibility to different Leishmania, and the subgenus Viannia (braziliensis complex) is notoriously of limited pathogenicity in most animal models, cross-immunity as evidence by diminished pathology, is not a simple matter to evaluate. Nevertheless, our experience with human infection indicates that individuals who have had disease

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due to *L. (v) panamensis* remain susceptible to re-infection with closely related organisms (distinct zymodeme or schizodeme) of the same taxon as well as to *L. (v) braziliensis* (Saravia et al. 1990. Lancet Vol. 336: 398-402). Re-activation of infection and the appearance of new lesions following resolution of disease with or without specific treatment, suggests that even immunity acquired to the homologous organism may not protect against further disease. It will be pertinent to determine the risk factors for recurrent disease so that appropriate control measures may be targeted to the prevention of recurrence.

There is increasing evidence for the latent persistence of *Leishmania* infection. Since subclinical infections probably outnumber clinically apparent infections, it will be important to define the potential contribution of subclinical infection to herd immunity, as a source of further transmission, and future disease.

Exogenous re-infection and the incidence of disease in individuals having a prior positive skin test argues against the notion of premunition as a mechanism of protection in American tegumentary leishmaniasis due to the *viannia* subgenus.

3. **Who is susceptible to leishmaniasis? How can susceptible individuals be identified?**

Lack of understanding of the natural history of human leishmaniasis restricts our ability to precisely define susceptibility, particularly in terms of disease. An operational definition of susceptibility based on the absence of immunological evidence of prior exposure to *Leishmania* may provide a reasonable approximation of susceptibles with respect to infection. Although further investigation is needed in order to determine whether individuals with well-defined clinical "phenotypes" reflect intrinsic host differences in disease susceptibility, chronic and/or recurrent disease may provide an indicator of susceptible individuals.

4. **Does the immune response participate in the pathogenesis of tegumentary leishmaniasis?**

Direct evidence for the participation of T lymphocytes in the progression of disease had been obtained in the inbred mouse model of tegumentary leishmaniasis caused by *Leishmania major*. Phenotypically distinct subpopulations of T lymphocytes have been shown to adoptively transfer either protective or disease enhancing response to *L. major*. In human infection with *Leishmania* of the *viannia* subgenus, non-resolving, chronic disease is associated with immunologic hyper-reactivity. Likewise, mucosal disease is associated with increased cellular and antibody responses to *Leishmania* antigens. These patterns of response provide evidence, albeit indirect, for the participation of the immune response in the pathogenesis of human tegumentary leishmaniasis.
5. **Can a non-healing or non-protective response be converted to a healing or protective response? How? Which antigens, preparation, route?**

Elegant experiments by Howard, Hale and Liew established that the healer and non-healer phenotype of *L. major* infection in inbred mice is determined by hematopoietic cells and that the selective ablation of radiation sensitive cell populations could convert the non-healer to a healer phenotype. Other investigators have subsequently shown that a variety of immunomodulatory treatments can also reverse the non-resolving progression of *L. major* infection in the highly susceptible BALB/c strain. The immunotherapy experience of investigators of the Instituto de Biomecidina in Venezuela led by Dr. Jacinto Convit, (Convit et al., 1987. Lancet Vol 1:401-404) indicates that a healing response can be induced in patients infected with *Leishmania* of the *viannia* subgenus by the administration of leishmanin and BCG. Even chronic lesions characterized by a hyperreactive cutaneous response to *Leishmania* antigens were shown to heal following this immunologic "perturbation" of a non-resolving response to *Leishmania* infection. While it remains to be determined whether immunotherapy results in resistance to new disease, it is clear that the untoward effects of the immune response can be reversed to the benefit of affected patients. This intervention may be optimized by the utilization of defined antigens and alternative adjuvants.

6. **How can acquired resistance be assessed? Which immune response parameter correlates with protection?**

Assessment of resistance is precluded by an understanding of the pathogenesis of leishmaniasis as well as the immunologic basis of resistance to disease. Neither cell-mediated nor antibody responses to whole antigen preparations are correlated with resistance, i.e. protection from new infection and disease in man. Since protective and exacerbative T lymphocyte subpopulations are preferentially induced by distinct antigen fractions (Scott et al. 1988. J. Exp. Med. 168:1675-1684) resistance may correlate with the qualitative response to defined antigens or even epitopes. In any case the identification of immunologic correlates of resistance is a priority concern since it would allow populations to be classified as susceptible or resistant and vaccine efficacy to be expeditiously evaluated.

7. **What exactly would we hope to prevent by immunoprophylaxis? Chronic disease, any disease?**

If individuals who have already acquired infection contribute to the disease burden in endemic areas, alternative control measures will be needed to prevent the progression of latent infection to disease. Are or can humans be reservoirs or "carriers" of infection? If so could immunization prevent them from becoming reservoirs?
The prevention of severe disease alone may justify vaccination. If all or most disease cannot be prevented, length of treatment might conceivably be shortened for lesions developing in immunized individuals. Reasonable and achievable goals should be set for the immunoprophylaxis of New and Old world leishmaniases in accordance with the disease burden and natural history of the parasites involved.

Immunological Considerations in the Control of Leishmaniasis
By
F.J. Andrade-Narvaez, G. Valencia-Pacheco; M.R. García-Miss

Introduction

There is a great volume of information regarding immunological studies of the Leishmaniasis, including clinical and experimental, ranging from applied research such as development of new diagnostic tools up to very basic research on immunogenetics and molecular biology studies. For the last 10 years excellent reviews of this field have been done (1-4). However, examination of the role of immunological consideration in the control of the Leishmaniasis has been rare.

Objectives

On this basis, it has been considered neccessary to carry out a review of our experience studying Mexican Localized Cutaneous Leishmaniasis (Mex LCL), well known as "Chiclero's Ulcer" (5). The immunological aspects incorporated into our Leishmaniasis Programme have the following objectives:

- To develop new immunological diagnostic tools.
- To identify host risk factors associated with clinical outcome.
- To study host-parasite relationships.
- To characterize the immune response.
- To develop vaccine "candidates".

State of the Art

Development of new immunological diagnostic tools: The first task was to develop an enzyme-linked immune assay (ELISA test) to detect IgG antibodies to L. mex. mex. determining its sensitivity and specificity. A total of 223 human sera were assayed and results obtained, including "chronic" cases (low positivity of 54%), which are relevant due to the fact that they are useful to support the diagnosis of Mex LCL. Serodiagnosis by ELISA has been positive in the study of Leishmaniasis both in the Old World (6-9) and in the New World (10-12). This preliminary study proved to be useful as a contributory diagnosis method in cases of suspected Mex LCL (13).