Part II. Leishmaniasis: Cell Biology and Immunology

Chaired by Professor D J Bradley

**Part II.I *Leishmania*/Macrophage Interactions:
their role in determining Host Response
to Leishmanial infection.**

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Early workers identified host macrophages as the site of intracellular parasitisation by leishmanial parasites. Several phases in the interaction between these parasites and macrophages have since been identified which may be crucial in determining the outcome of an infection.

Firstly, since *Leishmania* species are obligate intracellular parasites of the monocular phagocyte system, they must first be targetted to and gain entry into a permissive subpopulation of macrophages. This depends upon receptor/ligand binding between parasite and macrophage and transmission of transmembrane signals to promote a phagocytic response. Certain receptor/ligand interactions may also promote transmission of signals which trigger a respiratory burst response and the release of potentially harmful oxygen metabolites.

In their interaction with murine resident peritoneal macrophages, promastigote forms of the parasite bind via complement and lectin-like receptors and elicit a strong respiratory burst response. Amastigotes appear to be less dependent upon entry via these receptors and fail to elicit a significant respiratory burst response. They are also more resistant to the products of respiratory burst activity.

After internalisation, genetically controlled variations in the ability of host macrophages to control parasite multiplication may also have a profound effect upon the subsequent course of infection. Innately resistant macrophages control parasite proliferation keeping the parasite load to a level which promotes development of an effective T-cell mediated immune response, resulting in production of gamma interferon and other lymphokines which activate macrophages to kill the parasite. This, in turn, is dependent upon presentation of parasite antigen in association with MHC products by macrophages and macrophage-like dendritic cell populations.

Polymorphism of genes encoding MHC class II molecules also influences disease profiles during the course of infection. Innately susceptible macrophage populations yield high parasite loads which may, in association with particular MHC class II molecules, paralyse the host's immune response by shifting the balance towards the suppressor arm of T-cell regulated responses.

Part II.II Immunological Control and Vaccination

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Vaccination against the cutaneous forms of leishmaniasis has long been practised. Accounts in the literature suggest that from as early as the 19th century children in Baghdad had been vaccinated against "Oriental sore", by inoculating material from active human lesions by excoriating the skin of the arm or thigh (Wenyon, 1911). In this way long-lasting immunity could be induced and the face could be saved from disfiguring scars. Until recently a similar form of vaccination using replicating cultured *L. major* promastigotes had been widely used in the USSR and Israel. However, the use of live material is subject to obvious drawbacks, scarring is inevitable at the site of inoculation and there is always the possibility of a particularly susceptible recipient developing a chronic or severe infection. For this reason the above two programmes have been largely discontinued and large scale vaccination using living organisms remains progress only in Iran.

The Protective Usefulness of Attenuated Vaccines

The problems inherent in the use of virulent vaccines have stimulated trials using attenuated parasites or parasite fractions. Although these have proved disappointing with regard to Old World cutaneous leishmaniasis, recent field trials in South America have produced promising results. Using a vaccine consisting of equal parts heat-killed and sonicated promastigotes from five different parasite isolates, Mayrink *et al.* (1985) successfully and significantly protected from infection approximately 70% of the participants that became skin-test positive following vaccination.

There are few vaccination studies on human visceral leishmaniasis caused by *L. donovani*. However, Manson-Bahr (1961) has reported that a ground squirrel strain of *L. donovani* did not visceralise following intradermal infection and protected three volunteers against subsequent challenge with human *L. donovani*. The ground squirrel parasite has, in fact, been identified as *L. major* using biochemical and serological methods (Chance *et al.*, 1978). Cross-immunity between species of *Leishmania* is not uncommon and is a point on which I shall elaborate further.