Pathogenesis of leishmaniasis

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General aspects

There are striking similarities in the immune responses generated against Leishmania and *Mycobacterium leprae* organisms. This is to be expected since both are obligate intracellular single cell organisms. In both, organisms are able to avoid immune surveillance and destruction. The persistent antigenic stimulation, as a result of persistence of the organisms leads to the establishment of cell mediated response characterized by granulomatous inflammation.

Inoculation of promastigotes initiates a chain of immunological responses which will ultimately determine the clinical presentation be it self-healing, persistance, and dissemination.

Innate immune responses

At the time of inoculation pattern recognition receptors activate a number of innate immune responses. This includes both secretory soluble molecules (complement) signaling (toll like receptors) and accumulation of innate immune cells. The latter includes neutrophils, monocytes macrophages sand natural killer cells. As the organisms continue to enter the macrophages very quickly, they manage to avoid the innate immune responses.

Adaptive immune responses

The phagocytic cells that have engulfed the organisms manage to destroy some of the organisms and generate specific leishmania antigens, which when presented to T helper cells generate a more organized and focused response aimed at controlling and destroying the organisms. This is a specific cell mediated immune response. The activated CD4 cells, macrophages along with the cytokine milieu generated determine the ultimate outcome.

Generation of Th1 response and their cytokines(IFNγ, TNFα) is associated with self-healing disease. IL-12 play a key role in generating a robust Th1 response. A Th2 response with opposing Th1 action will be associated with non-healing and dissemination.

At the same time, macrophages and chemokines like monocyte chemo-attractant protein (MCP-1), monokine induced by interferon gamma (MIG), IFNγ inducible protein 10(IP 10) and small amounts of macrophage inflammatory protein Ia (MIP Ia) invade sites of the infection in the dermis. MCP-1 expression is associated with self-healing cutaneous leishmaniasis (CI). MCP-1 act synergetically with IFNγ to enhance macrophage clearing of the Leishmania parasites. IL4 on the other hand has an opposing effect on MCP-1, allowing the Leishmania parasites to survive.

IFNγ induced macrophage activation further leads to two important downstream effects

1. Further enhancement of Th1 responses by way of IL 12
2. Killing of intracellular Leishmania parasites

1. The Th1 response

The role of a strong Th1 response as a protective immune response against Leishmania in CL is well established. Th1 cytokines mentioned above act synergertically with other cytokines (eg: Il-18, IL-23) is to induce Th1 cell differentiation and proliferation leading to clonal expansion of Th1 cells which in turn secrete IFNγ thus completing a positive feedback loop. Thus a strong Th1 response leads to resolution of infection.

2. Killing of intracellular parasites

This is achieved by two different mechanisms.

a) An IFNγ generated by above mentioned mechanisms generate signals which are able to regulate superoxide (O_{2^-}) and nitric oxide (NO) production and parasite killing by the macrophages. NO is believed to be directly cytotoxic in Leishmania parasites. The same

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mechanism is used by NK cells in the early stages of innate response in a weaker manner. Thus NO pathway appears to be the common mechanism of killing intracellular forms of Leishmania parasites.

b) Fas/FasL interaction

Activated Th1 cells induce apoptotic cell death in target cells expressing fas protein. IFNγ promotes fas expression on membrane surface of macrophage infected with Leishmania, making them susceptible in CD_4 cell induced apoptotic cell death.

This mechanism helps to limit the number of macrophages available for the promastigotes to replicate.

Non healing cutaneous leishmaniasis

The Th1/Th2 paradigm has drastically improved our understanding of adaptive immune responses involved in intracellular infections like Leishmaniasis. It can be argued that the Th1 response mentioned above if inadequate will allow persistance of the organisms and non-healing disease.

Immune mechanisms involved in persistent infections are mainly available in relation to L. major. It is clear that Th2 responses including IL-4 is associated with progressive disease. The disease progression is further promoted by IL-10 by suppressing the production of IL-12. IL-12 as mentioned earlier is the main driving force in the generation of a strong Th1 response and a weakened response is naturally associated with amastigote proliferation and persistence of the infection. TGFβ produced by T regulatory cells are also known to be suppression of protective mechanisms.

Paradox of Th1 and Th2 in visceral leishmaniasis (VL)

The dichotomy of Th1 and Th2 responses induced by Leishmania parasites is even less clear in VL. It is generally accepted that disease progression in VL is due to failure of the Th1 responses than due to an exaggerated Th2 response.

In patients with active VL the cytokine profile is not clearly polarized and both Th1 and Th2 cells appear to proliferate. In symptomatic patients the Th1 cytokines production is not suppressed but there is unresponsiveness of the effector cells. It is believed that high production of IL-10 contribute to this.

Recently more attention has been paid to the role played by IL-15 in VL. It is known that IL-15 has a suppressive role on Th2 responses though it has no direct stimulatory effect on Th1 cells. Thus the protective role of IL-15 emanate from an indirect effect on Th1 responses (weak Th2 responses enhance Th1 responses). IL15 by inducing the production of IL-12, also promotes anti-leishmaniasis activity of the Th1 responses.

Thus it can be summarized that healing is associated with secretion of IL-12 whereas IL-10 and not IL-4, with its negative effect on Th1 responses that leads to a fatal outcome.