Organ Specific Immunity in Visceral Leishmaniasis

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Experimental infection with L. donovani is characterized by distinct organ-specific immune responses [1]. The liver is the site of an acute resolving infection, minimal tissue damage and resistance to reinfection, whereas the spleen becomes a site of parasite persistence. Infection results in an impaired cell-mediated immune response that is associated with decreased Th1 cytokine production [2]. Both CD4+ and CD8+ T cells are activated following L. donovani infection [3], and both Th1 and Th2 responses are generated [4,5]. Broadly speaking, CD4+ T cells play a key role in controlling hepatic parasite growth in a primary infection [6,7], whereas CD8+ T cells are critical for rapid resolution of infection in the liver following rechallenge [8]. Control of hepatic infection in mice requires a coordinated host response involving the development of cellular infiltrates known as inflammatory granulomas around infected macrophages [9].

The development of hepatic granulomas during VL requires IL-12 dependent IFN γ production by T cells for the activation of monocytes and T cells [10]. In the granuloma, IFN γ is required for the optimal activation of infected KC (kupffer cells) and the generation of leishmanicidal mechanisms. As a result of T-cell dependent macrophage activation, reactive oxygen intermediates (ROI) and reactive nitrogen intermediates (RNI) are generated. Of the many cytokines involved in granuloma formation, moderate levels of TNF also clearly make a major contribution to the resolution of hepatic infection, and TNF expression is readily observed on infected KC at both early and late stages of the hepatic response [11]. TNF is essential for leucocyte recruitment to the liver and subsequent granuloma [12,13]. TNF is also required for host survival in murine models of VL, and TNF-deficient mice die within 2 months of infection with extensive hepatic necrosis and neutrophil infiltration, one of the rare situations in mice in which L. donovani infection is fatal [14]. In contrast, the spleen and bone marrow become chronically infected by mechanisms that are less well understood. In the mouse, the spleen becomes grossly enlarged and can account for up to 15% of body weight within 6–8 weeks post-infection. Parasite persistence is accompanied by a failure of granuloma formation, splenomegaly, disruption of lymphoid tissue microarchitecture including disruption of B-cell follicles and the marginal zone (MZ) [15], and enhanced haematopoietic activity. Similarly, postmortem examination of the spleen from VL patients has shown depletion of small lymphocytes, disintegration of the white pulp, and the absence of germinal centres (GC) [15].

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