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Pathogenic role of B cells and antibodies in murine *Leishmania amazonensis* infection

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Abstract

Leishmania amazonensis infection, occurring predominantly in Central and South America, can manifest itself in several forms, including those of cutaneous and diffuse cutaneous leishmaniasis. The outcome of *L. amazonensis* infection depends largely on host immune responses to the parasites. While $CD4^+$ T cell activation is a prerequisite for pathogenesis in *L. amazonensis*-infected mice, the roles of B cells and their antibody production are unclear. In this study, we provide evidence suggesting that B cells and antibodies are involved in disease pathogenesis. We documented a correlation between B cell activation and lesion progress in immunocompetent mice. In the absence of functional B cells and antibodies, JhD mice showed a delayed onset of disease and developed small lesions. Histological examination of these mice revealed a significant reduction in $CD4^+$ and $CD8^+$ T cells, but not in $MAC1^+$ macrophages, at the infection site. In contrast to the wild-type mice that showed typical tissue necrosis, *L. amazonensis*-infected JhD mice showed no or minimal signs of necrotic foci. A marked reduction in $CD4^+$ T cell proliferation and cytokine (IFN-γ and IL-10) production in infected JhD mice suggested an involvement of B cells and antibodies in the priming of parasite-specific T cells. This notion was further supported by the observations that adoptive transfer of B cells or antibodies could restore $CD4^+$ T cell activation and migration in infected JhD mice. Moreover, antibody coating of parasites could stimulate dendritic cells to produce high levels of cytokines and increase their ability to prime naïve $CD4^+$ T cells. Since $CD4^+$ T cells are crucial to disease pathogenesis, this study suggests that B cells and their antibody production enhanced *L. amazonensis* infection, partially by promoting T cell priming and cellular migration to the infection site.
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1. Introduction

Leishmaniasis, a vector-borne disease caused by parasites of the *Leishmania* genus, is endemic in Africa, Asia, Europe and Central and South America. *Leishmania* infection can lead to various clinical manifestations ranging from benign, self-healing cutaneous lesions, and/or extensive, disfiguring mucocutaneous lesions to a life-threatening visceral infection. These diverse outcomes of the disease are determined by both the genetic composition of the various parasite species and host immune responses to the infection. Studies of host defense mechanisms are, therefore, essential to our understanding of the disease pathogenesis caused by *Leishmania* infection. While many studies have focused on and demonstrated the integral roles of $CD4^+$ T cells, dendritic cells (DCs) and macro-

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phages (MΦs) in *Leishmania* infection, less emphasis has been placed on understanding how B cells and their antibody production may influence the outcome of infection.

Despite evidence of active B cell activation and antibody production during the progressive disease in human (Galvao-Castro et al., 1984; Hailu et al., 2001; Miles et al., 2005) and murine models (Howard et al., 1980; Palanivel et al., 1996), the biological functions of B cells and antibodies in cutaneous leishmaniasis remain a matter of debate. Several lines of evidence using *Leishmania major* infection as a model have suggested that B cells can enhance disease pathogenesis. These studies include those that showed disease exacerbation following an IL-7-mediated B cell expansion in susceptible BALB/c mice (Hoerauf et al., 1995) and a decrease in disease progression in B cell-deficient JhD mice (Miles et al., 2005). Moreover, the IgG immune complex was also shown to reduce leishmaniacidal activity by inducing high levels of IL-10 production by MΦs (Anderson et al., 2002; Miles et al., 2005). While the above studies strongly suggest pathogenic roles for B cells and antibodies, other studies have suggested that B cells and/or antibodies play a protective role during *Leishmania* infection. For example, Scott et al. (1986) and Woelbing et al. (2006) demonstrated that deletions of B cells either via anti-IgM treatment or targetted gene deletion (μMT) could increase the disease pathogenesis caused by *L. major* infection in otherwise resistant C3H/HeN and C57BL/6 mice. On the other hand, some reports have suggested that B cells and antibodies do not play any significant role during the course of *L. major* infection, as evidenced by comparable disease outcomes and T cell responses in B cell-deficient μMT mice and their wild-type counterparts on both C57BL/6 and BALB/c backgrounds. Similar observations were documented using anti-IgM-treated C3H/HeJ mice (Sacks et al., 1984; Brown and Reiner, 1999).

The observed discrepancies in the involvement of B cells may be attributed to multiple factors, including the host's genetic background, infection routes and doses, specific growth characteristics and differential host immunosuppressive mechanisms employed by individual parasite species and strains. While the results obtained from studies of the *L. major* infection model have been variable, studies of B cell functions using parasites of the *Leishmania mexicana* complex have provided more consistent conclusions. B cells and/or antibodies have been suggested to enhance disease pathogenesis in *L. mexicana*, *Leishmania pifanoi* and *Leishmania amazonensis*. For example, studies by Kima et al. (2000) have shown that, when infected with either *L. pifanoi* or *L. amazonensis,* JhD mice that lack functional B cells and antibodies displayed a reduced lesion size, compared with that of wild-type counterparts. Focusing on an *L. pifanoi* infection model, Colmenares et al. (2002) subsequently demonstrated that the presence of antibodies is associated with active cellular recruitment at the infection site. While this study suggested the induction of cell infiltration as a potential mechanism by which antibodies can enhance disease pathogenesis in *L. pifanoi* infection, it remained to be investigated whether this mechanism can explain the disease pathogenesis caused by other species of the *L. mexicana* complex. Given the diversity in genetic backgrounds of these parasites and the various disease symptoms these can cause, we further investigated the mechanisms of B cells and antibodies in disease pathogenesis caused by another member of the *L. mexicana* complex, *L. amazonensis*.

Cutaneous leishmaniasis caused by *L. amazonensis* can lead to non-healing lesions in all tested inbred strains of mice; however, varying degrees of severity have been observed (Cupolilo et al., 2003; Qi et al., 2001; Vanloubbeeck and Jones, 2004). While the cellular mechanisms responsible for this generalised susceptibility of mice to *L. amazonensis* infection are unresolved, $CD4^+$ T cells are known to play an integral role in lesion development and disease pathogenesis (Soong et al., 1997; Jones et al., 2000). Mice deficient in functional $CD4^+$ T cells ($RAG2^{-/-}$ and MHC class $II^{-/-}$mice) did not develop lesions of an appreciable size, even at late stages of infection (Soong et al., 1997). While it is clear that $CD4^+$ T cells are required for disease pathogenesis, it appeared that other cellular components also contribute to disease formation, because $RAG2^{-/-}$ mice that were adoptively transferred with unfractionated splenocytes developed more progressive lesions than did mice that received purified $CD4^+$ T cells alone (Soong et al., 1997). Therefore, other host immune components, such as B cells and/or antibodies, are potentially involved in disease development following *L. amazonensis* infection.

In this study, we assessed the pathogenic roles of B cells and antibodies during *L. amazonensis* infection by examining parasite-specific cellular immune responses in two immunocompetent mouse strains with different disease susceptibilities, as well as in JhD mice that lack functional B cells due to targetted deletion of the J segments of the Ig heavy chain. We found that B cells do play significant roles in disease formation, in particular in the induction of local cellular recruitment and the priming of parasite-specific $CD4^+$ T cells. Since $CD4^+$ T cells in *L. pifanoi*-infected JhD mice displayed normal proliferative responses (Colmenares et al., 2002), B cell involvement in the priming of $CD4^+$ T cells appeared to be unique to *L. amazonensis* infection. A restoration of T cell activation and migratory functions following adoptive transfer of B cells or passive transfer of immune sera into JhD mice further suggests that B cells could assist in the activation of $CD4^+$ T cells via both antibody-dependent and antibody-independent mechanisms. In vitro examination of antibody-mediated priming of $CD4^+$ T cells also revealed that antibodies could enhance the ability of DCs to prime naïve $CD4^+$ T cells. Since the priming of parasite-specific $CD4^+$ T cells is required for disease pathogenesis (Soong et al., 1997), B cell-mediated enhancement of $CD4^+$ T cells could directly contribute to disease pathogenesis. Collectively, this study provides evidence of various mechanisms in which B cells and their

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