Minireview

Type 1 and type 2 responses to Leishmania major

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Received 10 September 2001; received in revised form 14 January 2002; accepted 14 January 2002

First published online 15 February 2002

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Leishmania major is a protozoan parasite that is transmitted to the mammalian host by its sand fly vector when the fly probes in the host's skin for a blood meal and injects the parasite within its saliva. In mice experimentally infected with L. major, outgrowth of CD4 type 1 (Th1) cells leads to resolution of the infection, but outgrowth of type 2 (Th2) cells exacerbates disease. To design an effective vaccine against the parasite (and other pathogens that induce polarized Th1 and Th2 responses), we must determine the mechanism underlying this phenomenon so that we can design the vaccine to elicit the appropriate (i.e., protective) Th cell. Recent work indicates that Th bias is influenced by a number of signals delivered by antigen-presenting cells, including cytokines and co-stimulatory molecules. Moreover, recent work also suggests that sand fly saliva influences the immune response to L. major and Th polarization. Determining the mechanisms that lead to polarized Th responses should expand our knowledge regarding immunity to L. major, and should add to our understanding of immunoregulation in general.

Keywords: Leishmaniasis; Th cell; Antigen-presenting cell; Cytokine; Co-stimulation; Sand £y

1. *Leishmania* . . .

Members of the genus Leishmania are sand £y-transmitted protozoan parasites that cause leishmaniasis in their vertebrate hosts. The parasite is transmitted to the host when the sand £y vector probes in the skin for a blood meal and injects the promastigote form of the parasite within its saliva. Importantly, the saliva dramatically enhances the infectivity of the parasite for the host. When a large number of parasites (10^4^10^6) are injected into experimental mice, saliva markedly enhances infection compared to the infection in saliva-free control animals. When the number of parasites injected by the sand £y (~100) is injected, the parasite does not survive unless it is co-injected with sand £y saliva [1]. Thus, saliva may be critical for natural transmission of Leishmania by sand £ies. Sand £ies that transmit the parasite in the Old World are of the genus Phlebotomus and those that transmit Leishmania in the New World are of the genus Lutzomyia.

Leishmaniasis currently a¥icts some 12 million individuals, with 350 million at risk [2]. In addition, HIV has compounded the acquisition/re-activation of leishmaniasis, and recent epidemics of leishmaniasis in such places as Sudan have been particularly devastating [2]. Moreover, there are still no e¡ective control measures for the disease.

Within the mammalian host Leishmania resides as an amastigote in phagocytic cells such as macrophages, dendritic cells and neutrophils (reviewed in [3^5], space limitations do not permit a thorough survey of the literature). The clinical manifestations of leishmaniasis depend not only upon the species of parasite infecting the host, but genus

a lesion at the site of the insect bite, which takes months to

sequent work (with one exception, [16]) con¢rmed that

in turn these cells can stimulate many T cells due to the large surface area of the dendritic cells. In contrast to the bene¢cial e¡ects of IL-12, IL-4 is perhaps most responsible for disease progression in mice infected with L. major. As discussed above (Section 2), an early anti-LACK response in susceptible BALB/c mice leads to production of IL-4, down-regulation of IL-12 receptors and ultimately death of the mice [3^5]. In addition, treating with IL-12 or with anti-IL-4 allows BALB/c mice to heal an infection with L. major [3^5], which demonstrates how these two cytokines can literally have life or death e¡ects in infected mice.

However, in addition to IL-12 and IL-4, several other cytokines have marked e¡ects on infection with L. major in mice (Fig. 1). For instance, tumor necrosis factor (TNF)-α is critical for resolution of a L. major infection since infection with the parasite in TNF-α knockout mice is fatal [23]. Among the many ways in which TNF-α may play a role, the most obvious is its ability to enhance macrophage activation, NO production and thus parasite clearance. Similar to IL-12 and TNF-α, IFN-α/β is also produced by antigen-presenting cells. IFN-α/β (also known as type 1 IFN) can induce cell activation, including

munomodulatory properties of sand £y saliva that are involved in this phenomenon, the reader is referred to Gillespie et al. [32] or Kamhawi [33].

The immunomodulatory properties of whole saliva (from either Old or New World sand £ies) or of maxadilan (or MAX, a potent vasodilator/immunomodulator present in the saliva of New World sand £ies) would be expected to exacerbate leishmaniasis (summarized in Table 1), and thus could be the explanation for the e¡ect of saliva/MAX on infection with L. major. For example, saliva increases IL-4 production, and IL-4 is one of the most important factors that leads to disease progression in L. major-in-

liva and/or salivary MAX inhibits IFN-γ

fection and vaccinate against experimental cutaneous leishmaniasis. Eur. J. Immunol. 30, 3498^3506.
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