Role of Cytokines in Leishmaniasis

Dr. Heena Sachdeva [1], Dr. Manish Sharma[2]

A number of immunoregulatory cytokines are also produced in the developing granuloma in leishmaniasis. These cytokines are required to balance the successful development of protective immunity in the liver and prevention of associated immunopathology [1]. While euthymic L. donovani infected BALB/c mice are able to control infection with granuloma formation and IFN-γ and IL-2 production, nude BALB/c mice neither form granulomas nor produce IFN-γ [2]. Human recombinant IFN-γ restores the ability of nude BALB/c mice to control L. donovani infection. Furthermore, anti-IFN-γ antibody abolishes granuloma formation [3], confirming the importance of this cytokine in protection. Moreover, depletion experiments using anti-IL-2 monoclonal antibodies and reconstitution using recombinant IL-2 showed a role for IL-2 in leishmanicidal activity apparently through the induction of IFN-γ, and in granuloma formation with involvement of L3T4+ and Lyt 2+ T cells [4]. In one study, besides predominant IFN-γ production in the initial and late phase of infection, IL-4 production was detected in the intermediary phase coinciding with peak of parasite burden in the susceptible strain, and no IL-4 production in the resistant mouse strain [5]. Nevertheless other studies contradicted these findings. No IL-4 or IL-5 production was observed in three different strains of mice infected with L. donovani, and in the liver, only IFN- γ RNA was detected by Northern blot, and both Th1 and Th2 cytokine mRNAs, IL-4, IL-10, IFN-γ and IL-2 mRNA were detected by PCR [6]. Furthermore, mice treated with anti-IL-4 monoclonal antibodies and mice with IL-4 gene disruption [7] did not show better control of the infection.

IL-10, another Th2 cytokine, however, was related to progressive disease in human visceral leishmaniasis [8] and was shown to have a role in susceptibility to experimental visceral leishmaniasis. A progressive increase in IL-10 mRNA level in tissues during infection suggested a role in susceptibility [9]. In addition, the control of parasite growth in inner organs in BALB/c IL-10-/- mice and in normal mice with IL-10 receptor blockade by antibodies confirmed the role of IL-10 in susceptibility [10]. Since IL-10 receptor blockade increased serum IFN-γ levels, a protective effect was initially attributed to the non-suppressed leishmanicidal effect of IFN-γ. However, suppression of parasite growth with IL-10 receptor blockade even in IFN-γ gene-disrupted mice suggested a broader effect of IL-10 on the suppression of multiple leishmanicidal mechanisms [11]. In L. major-infected resistant C57BL/6 mice, IL-10 was shown to be important for the persistence of the parasite in the lesion, preventing its complete clearance from the lesion despite the presence of a protective immune response [12]. Furthermore, this apparently undesirable persistence of the parasite was shown to be of utmost importance for the maintenance of protective immunity against re-infection, with CD4+CD25+ regulatory T cells with IL-10- dependent and IL-10-independent mechanisms probably involving transforming growth factor (TGF)-ß being involved in the suppression of IFN-γ production [13].In contrast, IL-12 has been shown to be linked to protection against the infection. IL-12 treatment of L. donovani-infected BALB/c mice significantly reduced the parasite burden with the participation of CD4+ and CD8+ T cells, NK cells and IFN-γ, IL-2 and tumor necrosis factor (TNF)-α [14].. But a distinct antimicrobial effect of IL-12, independent of IFN-γ, has also been demonstrated in experiments using IFN-γ gene-disrupted mice. These mice, as expected, showed a progressive infection for the first eight weeks but in the late phase developed a capacity to reduce the parasite burden with the participation of TNF- α induced by IL-12 [15].

REFERENCES

[1] M.L. Murphy, U. Wille, E.N. Villegas, C.A. Hunter, and J.P. Farrell, “IL-10 mediates susceptibility to Leishmania donovani infection”. Eur. J. Immunol. 31(10): 2001, pp.2848–2856.

[2] H.W. Murray, J.J. Stern, K. Welte, B.Y. Rubin, S.M. Carriero, and C.F. Nathan, “Experimental visceral leishmaniasis: production of interleukin 2 and interferon-gamma, tissue immune reaction, and response to treatment with interleukin 2 and interferon gamma. J. Immunol. 138(7): 1987,pp.2290–2297.

[3] K.E. Squires, R.D. Schreiber, M.J. McElrath,B.Y. Rubin, S.L. Anderson, and H.W. Murray, “Experimental visceral leishmaniasis: role of endogenous IFN-gamma in host defense and tissue granulomatous response”. J. Immunol. 143(12): 1989, pp.4244–4249.

[4] H.W. Murray, G.D. Miralles, M.Y. Stoeckle, and D.F. McDermott, “Role and effect of IL-2 in experimental visceral leishmaniasis. J. Immunol. 151(2):1993, pp. 929–938.

[5] S. Saha, S. Mondal, A. Banerjee, J. Ghose, S. Bhowmick, and N. Ali, “Immune responses in kala-azar. Indian J. Med. Res. 123(3): 2006, pp.245–266.

[6] G.D. Miralles, M.Y. Stoeckle, D.F. McDermott, F.D. Finkelman, and H.W. Murray, "Th1 and Th2 cell-associated cytokines in experimental visceral leishmaniasis". Infect. Immun. 62(3): 1994, pp.1058–1063.

[7] P.M. Kaye, A.J. Curry, and J.M. Blackwell, "Differential production of Th1- and Th2-derived cytokines does not determine the genetically controlled or vaccine-induced rate of cure in murine visceral leishmaniasis". J. Immunol. 146(8): 1991,pp.2763-2770.

[8] C.L. Karp, S.H. el-Safi, T.A. Wynn, M.M. Satti, A.M. Kordofani, F.A. Hashim, M. Haq-Ali,M., F.A. Neva, T.B. Nutman, and D.L. Sacks, "In vivo cytokine profiles in patients with kala-azar. Marked elevation of both interleukin-10 and interferon-gamma". J. Clin. Invest. 91(4): 1993, pp.1644–1648.

[9] P.C. Melby, Y.Z. Yang, J. Cheng, and W. Zhao, "Regional differences in the cellular immune response to experimental cutaneous or visceral infection with Leishmania donovani". Infect. Immun. 66: 1998,pp.18–27.

[10] H.W. Murray, C.M. Lu, S. Mauze, S. Freeman, A.L. Moreira, G. Kaplan, and R.L. Coffman, "Interleukin-10 (IL-10) in experimental visceral leishmaniasis and IL-10 receptor blockade as immunotherapy". Infect. Immun. 70(11): 2002, pp.6284–6293.

[11] H.W. Murray, A.L. Moreira, C.M. Lu, J.L. DeVecchio, M. Matsuhashi, X. Ma, et al. "Determinants of response to interleukin-10 receptor blockade immunotherapy in experimental visceral leishmaniasis". J. Infect. Dis. 188(3):2003, pp. 458–464.

[12] Y. Belkaid, K.F. Hoffmann, S. Mendez, S., Kamhawi, M.C. Udey, T.A. Wynn, and D.L. Sacks, "The role of interleukin (IL)-10 in the persistence of Leishmania major in the skin after healing and the therapeutic potential of anti-IL-10 receptor antibody for sterile cure". J. Exp. Med. 194(10): 2000, pp.1497-1506.

[13] Y. Belkaid, C.A. Piccirillo, S. Mendez, E.M. Shevach, and D.L. Sacks, "CD4+CD25+ regulatory T cells control Leishmania major persistence and immunity". Nature 420(6915): 2002, pp.502–507.

[14] H.W. Murray, and J. Hariprashad, "Interleukin 12 is effective treatment for an established systemic intracellular infection: experimental visceral leishmaniasis". J. Exp. Med. 181(1): 1995, pp.387–391.

[15] A.P. Taylor, and H.W. Murray, "Intracellular antimicrobial activity in the absence of interferon gamma: effect of interleukin-12 in experimental visceral leishmaniasis in interferon gamma gene-disrupted mice". J. Exp. Med. 185(7): 1997,pp.1231–1239.