A role for NK cells in innate immunity against human leishmaniasis

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Date: 2003-09-05

Location: Föreläsningssalen vid Mikrobiologiskt och Tumörbiologiskt Centrum, Theorells väg 1

Time: 9.30

Department: Mikrobiologiskt och Tumörbiologiskt Centrum (MTC) / Microbiology and Tumor Biology Center (MTC)

Abstract

Leishmaniasis is a group name for a spectrum of diseases caused by intracellular protozoa belonging to the family Leishmania. The parasites has been widely used as a tool to study the Th1 / Th2 paradigm of resistance and susceptibility in mice. A role of NK cells in leishmaniasis has been implicated, but not fully explored. In this thesis work we have continued previous studies exploring the cellular, in particular NK cell, responses to Leishmania antigens in blood mononuclear cells from humans with no history of leishmaniasis. It is of importance to study the responses in unexposed donors since they a) represent a potential group to whom a vaccine will be given and b) will give information about the innate responses to Leishmania, which may be of importance in determining disease outcome and/or protection. The last part of this work investigated the contribution of NK cells in the development of human cutaneous leishmaniasis. It has long been known that individuals who have healed from cutaneous leishinaniasis are protected against further disease. Thus, a vaccine against leishmaniasis would appear to be achievable. Vaccine studies performed on humans have shown that live Leishmania vaccine induces solid protection, while heat-killed Leishmania + BCG induce variable protection. We tested if the differences in the efficacy of the two types of vaccines were in part due to differential cellular responses initially induced by live and dead parasites. Results show clear differences in the type of responses evoked by live and dead parasites. Live promastigotes induced IFNgamma secretion in NK cells, while killed promastigotes tended to induce Me cells proliferation. Furthermore, we demonstrate that live promastigotes independent, of other cell subsets and IL-12, could induce NK cells to IFFgamma secretion, Suggesting that NK cells can contribute independently and very early on in the defence against pathogens. A number of vaccine candidates against leishmaniasis, such as Leish-111f, LACK (Leishmania homologue of receptors for activated C kinase) and the amastigote antigens P-2, P-4 and P-8, have demonstrated encouraging results in mice but, are yet to prove themselves in humans. We tested the stimulating capacity of P-2, P-4 and P-8 in healthy donors and found P-2 to have most reactivity. A similar pattern of reactivity, but with enhanced magnitude was observed when cells were stimulated with LACK. Both LACK and P-2 stimulated cells to proliferation and secretion of IFFgamma and IL- 10. Both T cells and NK cells were involved in these responses. Furthermore, we demonstrated that the induction of IFFgamma as well as proliferation to these vaccine candidates were MHC class 11 dependent, whereas IL- 10 secretion tended to be enhanced by blocking MHC class II. Direct activation of NK cells could not be achieved by LACK or P-2 requiring antigen presenting cells for induction of NK responses. NK cells have been implicated in protection and healing of cutaneous leishmaniasis. To follow up on these data and data from unexposed individuals we have evaluated the contribution of NK cells to IFFgamma response in cells from Iranian patients with active cutaneous leishmaniasis. Initial cross sectional studies indicated that purified NK cells from active cutaneous leishmaniasis patients had reduced ability to secrete IFNgamma compared to cells from healthy controls. Furthermore, in cured patients, Me cells appeared to downregulate the NK cell induced IFNgamma. However, when cytokines (IFNgamma and IL-13) were evaluated in a longitudinal study in individual donors before and after artificial infection we found that NK cells contributed significantly and equally to the cytokine response both before and nine months after infection, when most of the donors showed signs of disease. The choice of study group and infection dose may have contributed to these unexpected results. The cumulative results of the studies continue to suggest a role for NK cells in the control of leishmaniasis.

List of papers:

I. Nylen S, Mortberg U, Kovalenko D, Satti I, Engstrom K, Bakhiet M, Akuffo H (2001). "Differential induction of cellular responses by live and dead Leishmania promastigotes in healthy donors. " Clin Exp Immunol 124(1): 43-53 Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/11359441)

II. Nylen S, Maasho K, Soderstrom K, Ilg T, Akuffo H (2003). "Live Leishmania promastigotes can directly activate primary human natural killer cells to produce interferon-gamma. " Clin Exp Immunol 131(3): 457-67
Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/12605699)

III. Maasho K, Satti I, Nylen S, Guzman G, Koning F, Akuffo H (2000). "A Leishmania homologue of receptors for activated C-kinase (LACK) induces both interferon-gamma and interleukin-10 in natural killer cells of healthy blood donors. " J Infect Dis 182(2): 570-8. Epub 2000 Jul 24
Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/10915091)

IV. Nylen S, Maasho K, McMahon-Pratt D, Akuffo H (2003). "Leishmanial amastigote antigen P-2 induces MHC class II dependent NK cell reactivity in cells from healthy donors." (Submitted)

V. Nylen S, Eidsmo L, Mohammadi A, Khamesipour A, Akuffo H (2003). "NK cell responses in patients with cutaneous leishmaniasis." (Manuscript)

URI: http://hdl.handle.net/10616/39659 (http://hdl.handle.net/10616/39659)

Issue date: 2003-08-15

Publication year: 2003
ISBN: 91-7349-605-7

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