Concluding remarks

The immune privileged environment within the eye effectively blocks the induction and expression of immunity to a variety of pathogens. Because the eye and tumours share common pathways used to establish immune privilege, the study of ocular immunology and the immune response against tumours that form within the eye will provide important insights into how tumours escape and evade immune-mediated elimination.

Manfred Zierhut *is at the Dept of Ophthalmology, University of Tübingen, D72076 Tübingen, Germany;* ***Wayne Streilein*** *and* ***Bruce Ksander*** *are at the Schepens Eye Research Institute, Harvard Medical School, Boston, MA 02114, USA;* ***Hans Schreiber*** *is at the Dept of Pathology, University of Chicago, Chicago, IL 60637, USA;* ***Martine Jager*** *is at the Dept of Ophthalmology, Leiden University Medical Centre, 2300 RC Leiden, The Netherlands;* ***Dirk Ruiter*** *is at the Dept of Pathology, University Hospital Nijmegen, The Netherlands.*

References

1 Streilein, J.W., Ksander, B.R. and Taylor, A. (1997) *J. Immunol.* 158, 3557–3560
2 Apte, R.S., Sinha, D., Mayhew, E., Wistow, G.J. and Niederkorn, J.Y. (1998) *J. Immunol.* 160, 5693–5696
3 Singh, S., Ross, S.R., Acena, M., Rowley, D.A. and Schreiber, H. (1992) *J. Exp. Med.* 175, 139–146
4 Streilein, J.W., Niederkorn, J.Y. and Shadduck, J.A. (1980) *J. Exp. Med.* 152, 1121–1125
5 Kono, K., Salazar-Onfray, F., Petersson, M. *et al.* (1996) *Eur. J. Immunol.* 26, 1308–1313
6 Blom, D.J., Luyten, G.P.M., Mooy, C., Kerkvliet, S., Zwinderman, A.E. and Jager, M.J. (1997) *Invest. Ophthalmol. Vis. Sci.* 38, 1865–1872
7 Verbik, D., Murray, T.G. and Ksander, B.R. (1997) *Int. J. Cancer* 73, 470–478
8 Apte, R.S., Mayhew, E. and Niederkorn, J.Y. (1997) *Invest. Ophthalmol. Vis. Sci.* 38, 1277–1282

Can eradication of helminthic infections change the face of AIDS and tuberculosis?

Zvi Bentwich, Alexander Kalinkovich, Ziva Weisman, Gadi Borkow, Nulda Beyers and Albert D. Beyers

Helminth infections impair the host's immune response to HIV and tuberculosis (TB) and might contribute to the spread of these diseases. Thus, eradication of helminth infections may have a major impact on both HIV and TB in the developing world.

The reasons for the more rapid progression of human immunodeficiency virus (HIV) infection to AIDS in most developing countries are not at all clear. We have previously put forward the hypothesis that a major factor accounting for this difference is immune activation of the host caused by endemic infections, particularly helminthic infections[1]. These, we have argued, make the host more susceptible to HIV infection and less able to cope with it once infected.

Helminthic infections are common in vast regions of the world and, by the most conservative estimates, affect over a quarter of the world's population (~1.5 billion people)[2]. Thus, these chronic infections could have a major impact on the host's immune system and on the increased susceptibility and spread of HIV in the developing world. Following the same reasoning, together with more recent observations (detailed below), and given the similar geographic distribution of helminthic infections, HIV and *Mycobacterium tuberculosis*, we now hypothesize that helminthic infections may also decrease the host immune response to tuberculosis (TB) (Fig. 1). Furthermore, we argue that intestinal helminth infections might compromise the efficacy of vaccination for both HIV and TB. Thus eradication of helminthic infections from entire populations may have a major impact on both AIDS and TB in developing countries.

Helminthic infection and HIV

The immigration of Ethiopian Jews to Israel, some of them infected with HIV, provided us with a unique opportunity to test and support our hypothesis by the following findings.

(1) The vast majority of the Ethiopian immigrants were infested with helminths and had immune dysregulation with a dominant T helper 2 (Th2)-type immune profile that returned to normal with eradication of helminths[3,4].

(2) Peripheral blood mononuclear cells obtained from Ethiopian immigrants were highly susceptible to infection by HIV (Ref. 5).

(3) This susceptibility was associated with marked immune activation[6] and also with

PII: S0167-5699(99)01499-1

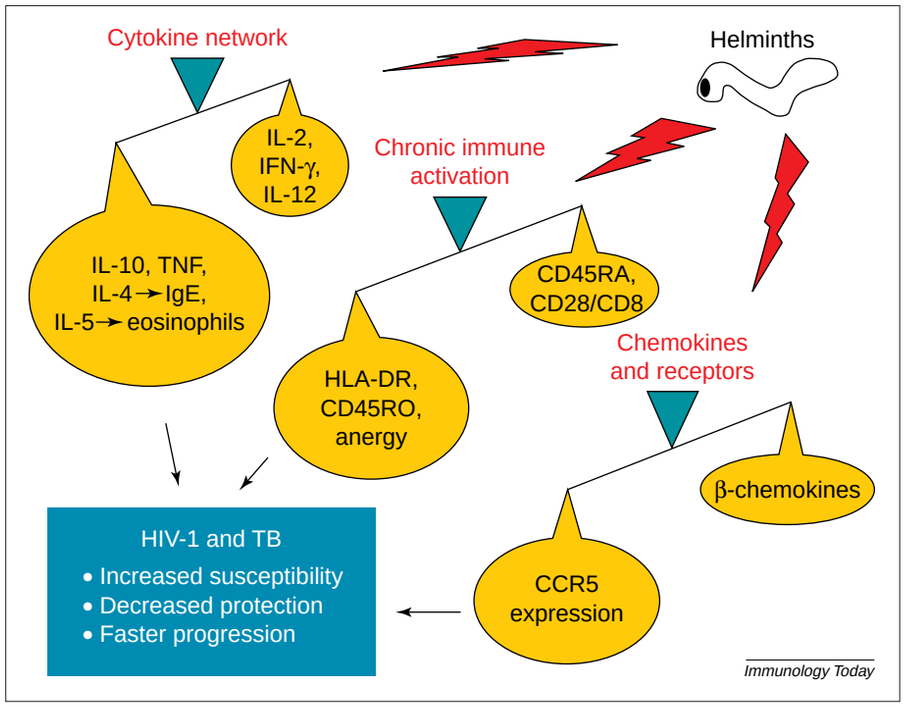

Fig. 1. *Chronic helminthic infection and its effects on HIV and TB susceptibility, disease progression and protection. Helminthic infections cause chronic immune activation and a strong T helper 2-type cytokine profile. Individuals infected with helminths have decreased* in vitro *β-chemokine secretion together with increased CCR5 expression on lymphocytes and monocytes. These changes in the immune system might increase the susceptibility to HIV and* Mycobacterium tuberculosis, *cause faster progression of these diseases, impair the host's protection against them and undermine the capacity to generate protective vaccines. Abbreviations: HIV-1, human immunodeficiency virus type 1; IFN-γ, interferon γ; IL-2, interleukin 2; TB, tuberculosis; TNF, tumour necrosis factor.*

increased expression of HIV co-receptors and decreased secretion *in vitro* of β-chemokines[23].

(4) The rate of progression of HIV infection, the plasma viral load, the immune activation profile and the response to highly active antiretroviral treatment in the Ethiopian immigrants were similar to that of non-Ethiopian Israelis once the helminth infections were eradicated when they were living in Israel[7–9].

(5) Preliminary results obtained in Ethiopia indicate that antihelminthic treatment decreases HIV plasma viral load (W. Dawit, unpublished).

Additional circumstantial evidence lends support to our hypothesis. First, similar immune activation and dysregulation of peripheral T-cell populations has recently been observed in Ethiopia[10]. Second, faster progression to AIDS has been documented in Africa, in areas endemic for helminths[11]. Third, increased plasma HIV viral load has been seen in helminth-infested regions in Africa[12], and finally, increased plasma HIV viral load is associated with Leishmaniasis and decreases following its treatment[13].

TB and the immune response

TB and HIV/AIDS share a number of common features, have a similar geographic distribution and each exacerbates the other[14]. In both diseases the onset is slow, the pathogens, localized within immune cells, evade and suppress the host immune response, and the host controls both infections by multiple mechanisms. The most important mechanism for the control of both pathogens is a Th1 immune response.

After infection with *M. tuberculosis*, more than 90% of individuals do not develop overt TB (Ref. 14). A strong interferon γ (IFN-γ) response to the organism is present in individuals who contain the infection, whereas this response is blunted in individuals with active TB disease[15,16]. Individuals lacking IFN-γ or IL-12 receptors are highly susceptible to mycobacteria, providing genetic evidence for the importance of a Th1 response for controlling mycobacterial infection[15].

The Western Cape region of South Africa has one of the highest reported incidences of TB in the world[17]. Detailed investigations in two adjacent suburbs of Cape Town reveal marked variation in the incidence of TB within these suburbs. The poorest subdistricts have the highest TB incidence. However, the driving force behind the epidemic cannot solely be attributed to crowding and rapid transmission of *M. tuberculosis*, because there is a preponderance of unique strains of the organism, indicating reactivation of latent infection[18]. Because the poor communities in this region are highly infested with helminths, particularly *Ascaris lumbricoides* and *Trichuris trichiura*, which induce potent Th2 responses with high IgE levels, we suggest that helminthic infection is a major environmental factor responsible for such reactivation.

Two studies lend support to these thoughts. First, a marked correlation was found between total serum IgE levels and the incidence of TB in the various subdistricts in Cape Town[19]. Second, total IgE and *Ascaris*-specific IgE levels were high in TB patients, and total IgE declined following successful treatment of TB (Ref. 20). Taken together, it is plausible that helminthic infections and Th2 dominance (manifested by high IgE levels) contribute to the high incidence of TB in Third World populations.

Protective immunity and helminthic infections

Several studies have shown that helminthic infections can affect the immune response to inciting antigens and pathogens, jeopardizing

Box 1. Research questions relevant to eradication of helminth infection

- Kinetics of changes and character of immune profile
- Generation of protective immunity to HIV and mycobacteria
- Change in incidence of TB and HIV infection
- Modulation of immunity by adjuvants
- Design and efficacy of protective vaccines

the host's ability to generate protective immunity to both HIV and mycobacteria (reviewed in Ref. 21).

(1) Schistosome-infected mice with a dominant Th2 immune profile have a Th2 'skewed' immune response to sperm whale myoglobin and to HIV envelope antigens, which is accompanied by downregulation of Th1 cytokines and an impaired cytotoxic T lymphocyte (Th1) response.

(2) The cytokine response to mycobacterial antigens can be modulated by helminth pre-induction of a Th2 response.

(3) Selective inhibition of T-cell subsets is seen in filariasis, in which T cells show antigen-specific anergy, while antibody responses remain intact.

(4) Humans infected with *Schistosoma mansoni* have an impaired tetanus toxoid Th1 response[22].

(5) Signal transduction, following *in vitro* stimulation of lymphocytes obtained from chronically immune-activated individuals, is downregulated, as is the proliferative response to purified protein derivative (PPD) and the delayed-type hypersensitivity response to bacille Calmette–Guérin (BCG) (G. Borkow *et al.*, unpublished).

The ability to generate HIV and TB protective vaccines depends very heavily on the ability to mount a potent cellular response and to test the efficacy of candidate vaccines in human field trials. Such trials can only take place in Africa and Asia, in areas with a high incidence of HIV and mycobacterial infections. Because the host immune background in the developing countries is biased towards a Th2 profile and chronic immune activation due to helminthic infections, the ability to mount a protective cellular response is likely to be diminished. In Africa and Asia, it is possible that the poor efficacy of BCG vaccination to confer protective immunity to TB is a reflection of the 'skewed' immune response of whole populations by endemic helminthic infections. It therefore becomes essential to take this major issue into consideration for the development of any protective vaccine.

Practical implications and unresolved issues

Eradication of helminthic infection on a large scale is feasible, relatively inexpensive and simple, and should become a priority for public health in developing countries. Indeed, the South African government has recently embarked on a large-scale helminth eradication programme involving over a million school children, with the purpose of correcting growth and cognitive impairments observed in helminth-infested populations[2]. We suggest here that deworming will also have a huge impact on the AIDS and TB epidemics. The questions that still need to be addressed, as part of such a programme, are manifold (summarized in Box 1). The kinetics of the changes of the immune profile following eradication of helminth infection, and the conditions necessary for them to persist are not yet completely clear. It is not known how deworming affects the incidence of TB and HIV infection (as we predict), and the generation of protective immunity to both infections. It is important to determine whether modulation of the immune response, such as by adjuvants, is possible in the presence of helminthic infections and following their eradication. Finally, it must be established whether helminth eradication makes a difference to the efficacy of vaccines for these infections.

We thank our co-workers and students for their diligence, and gratefully acknowledge support by the Institute of Advanced Therapy (IAT) for Center of Excellence in AIDS Research and the Horowitz Foundation to Z.B.; the KAMEA fellowship to A.K.; and the Glaxo Wellcome Action TB Programme and a Wellcome Trust Senior Research Fellowship to A.D.B.

Zvi Bentwich *(bentwich@agri.huji.ac.il),* ***Alexander Kalinkovich****,* ***Ziva Weisman*** *and* ***Gadi Borkow*** *are at the R. Ben-Ari Institute of Clinical Immunology, AIDS Center, Kaplan Medical Center, Hebrew University Hadassah Medical School, Rehovot, Israel;* ***Albert Beyers*** *(lb@gerga.sun.ac.za) and* ***Nulda Beyers*** *are at the Depts of Medical Biochemistry, and Pediatrics and Child Health/MRC Center for Molecular and Cellular Biology, University of Stellenbosch, PO Box 19063, Tygerberg 7505, South Africa.*

References

1 Bentwich, Z., Kalinkovich, A. and Weisman, Z . (1995) *Immunol. Today* 16, 187–191
2 Bundy, D.A.P. and de Silva, N.R. (1998) *Br. Med. Bull.* 54, 421–432
3 Bentwich, Z., Weisman, Z., Moroz, C., Bar-Yehuda, S. and Kalinkovich, A. (1996) *Clin. Exp. Immunol.* 103, 239–243
4 Bentwich, Z., Weisman, Z., Grossman, Z., Galai, N. and Kalinkovich, A. (1997) *Immunologist* 5, 21–26
5 Shapira-Nahor, O., Kalinkovich, A., Weisman, Z. *et al.* (1998) *AIDS* 12, 1731–1733
6 Bentwich, Z., Weisman, Z., Greenberg, Z., Nahmias, J., Stein, M. and Kalinkovich, A. (1998) *Clin. Exp. Immunol.* 103, 239–243
7 Galai, N., Kalinkovich, A., Burstein, R., Vlachov, D. and Bentwich, Z. (1997) *Lancet* 349, 180–181
8 Weisman, Z., Kalinkovich, A., Borkow, G., Stein, M., Greenberg, Z. and Bentwich, Z. (1999) *J. Acquired Immune Defic. Syndr. Hum. Retrovirol.* 21, 157–163
9 Bentwich, Z., Kalinkovich, A., Weisman, Z., Podolyako, M. and Galai, N. (1998) in *12th World AIDS Conference, Geneva,* pp. 191–195, Monduzzi Editore
10 Messele, T., Abdulkadir, M., Fontanet, A.L. *et al.* (1999) *Clin. Exp. Immunol.* 115, 443–450
11 Anzala, O.A., Nagelkerke, N.J.D., Bwayo, J.J. *et al.* (1995) *J. Infect. Dis.* 171, 686–689
12 Dyer, J.R., Kazembe, P., Vernazza, P.L. *et al.* (1998) *J. Infect. Dis.* 177, 1742–1746
13 Wolday, D., Berhe, N., Akuffo, H. *et al.* (1999) *Parasitol. Today* 15, 182–187
14 Coovadia, H.M., Jeena, P. and Wilkinson, D. (1998) *Int. J. Tuberc. Lung Dis.* 2, 844–851
15 Ottenhoff, T.H.M., Kumararante, D. and Casanova, J-L. (1998) *Immunol. Today* 19, 491–494
16 Torres, M., Herrera, T., Villareal, H., Rich, E.A. and Sada, E. (1998) *Infect. Immun.* 66, 176–180
17 Beyers, N., Gie, R.P., Zietsman, H.L. *et al.* (1996) *S. Afr. Med. J.* 86, 40–44
18 Warren, R., Hauman, J., Beyers, N. *et al.* (1996) *S. Afr. Med. J.* 86, 45–49
19 Beyers, A.D., van Rie, A., Adams, J., Fenhalls, G., Gie, R.P. and Beyers, N. (1998) *Novartis Foundation Symposium* 217, 145–157
20 Adams, J.F.A., Scholvinck, E.H., Gie, R.P., Potter, P.C., Beyers, N., Beyers, A.D. *et al.* (1999) *Lancet* 353, 2030–2033
21 Stadecker, M.J. and Hernandez, H.J. (1998) *Parasite Immunol.* 20, 217–221
22 Sabin, E.A., Araujo, M.I., Caravalho, E.M. and Pearce, E.J. (1996) *J. Infect Dis.* 173, 269–272
23 Kalinkovich, A., Weisman, Z., Leng, Q., Stein, M., Borkow, G. and Bentwich, Z. *J. Hum. Virol.* (in press)