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. 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). 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, 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. (2) Peripheral blood mononuclear cells obtained from Ethiopian immigrants were highly susceptible to HIV infection. (3) This susceptibility was associated with marked immune activation and also with a more recent observation (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).

References


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 helminthic infections may have a major impact on both HIV and TB in the developing world.
Helminthic infections cause chronic immune activation and a strong Th2-type cytokine profile. Individuals infected with helminths have decreased in vitro β-chemokine secretion, together with increased CC chemokine 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.

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 Th2 helper 2-type cytokine profile. Individuals infected with helminths have decreased in vitro β-chemokine secretion, together with increased CC chemokine 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.

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 response22.

(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 populations2. We suggest here that deworming will 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 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.

References