

GUEST COMMENTARY

Host Background Immunity and Human Immunodeficiency Virus Protective Vaccines, a Major Consideration for Vaccine Efficacy in Africa and in Developing Countries

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The AIDS epidemic is clearly the worst epidemic of the last century. Over 23 million individuals have already died from AIDS, and more than 36 million people are infected by human immunodeficiency virus type 1 (HIV-1), especially in Africa and Southeast Asia (36). It is estimated that more than 100 million people will be carrying the virus in less than 10 years (36). The only plausible way for diminishing this epidemic, aside from social and educational measures, is by mass vaccination. Regrettably, despite two decades of intensive efforts, no anti-HIV vaccine is yet available.

Two critical issues have to be considered as prerequisites for developing an effective HIV vaccine: first, what type of immune response is needed to confer optimal protection against HIV-1, and second, what is the role of the preexisting immune profile of the host in its capacity to mount a potent protective immune response following vaccination.

Regarding the first issue, it is probably true that although HIV-specific antibodies may play an important role in protection, the generation of HIV-specific cellular immunity, via a cellular-TH1 immune response, is a major requirement for a protective HIV vaccine (14, 24, 25). The role of TH1 and TH2 cells in controlling the immune response is well established (34), and their role in the pathogenesis of HIV has been studied extensively (19, 33, 40). Though there is controversy as to the role of TH1 versus TH2 in every phase of the infection (23, 40, 45), the following important findings clearly bear on this issue and support the central protective role of the TH1 response: (i) cytotoxic T lymphocytes (CTL) have a major role in the clearance of the primary HIV viremia during the acute phase of the infection and in maintaining low viremia during the asymptomatic phase of the infection (11, 28, 39); (ii) it has been suggested that progression of the infection is accompanied by a TH1-to-TH2 switch, with a reduction in the number of TH1 clones and an increase in the number of TH2 clones (16, 31); (iii) TH1 functions are correlated with better survival and slower progression (17, 40); (iv) TH2 cloned cells show increased susceptibility for HIV infection and replication (31), and, most importantly, (v) individuals who have been exposed to HIV and yet remain uninfected are HIV seronegative but

may have HIV-specific TH1-type immunity (17, 18, 22, 29, 30, 41), and HIV-seronegative infants born to HIV-infected mothers have HIV-specific CTL (1, 20). Finally, the importance of cellular immunity in conferring protection from infection has also been demonstrated in several studies of protective vaccination by simian immunodeficiency virus in primates (12, 38, 44).

Regarding the second issue, i.e., the role of host background immunity, the unique situation that occurred with the immigration of more than 50,000 Ethiopian Jews to Israel during the last 10 years has given us some very important insights. The vast majority of the new Ethiopian immigrants (ETH) had a dominant TH2 cytokine profile, with extremely high blood immunoglobulin E levels and eosinophilia (7, 8, 46). In addition, wide immune activation and dysregulation were found in them (7, 8, 27, 46): (i) lowered levels of CD4 and increased levels of CD8 T cells; (ii) significant increases in activated cells (HLA-DR⁺, and CD8⁺ CD38⁺) and in memory cell (CD45RO⁺) levels; (iii) decreases of naive (CD45RA⁺) and CD8⁺ CD28⁺ T cells; (iv) increased levels of spontaneous apoptosis; (v) attenuated phosphorylation of mitogen-activated protein kinase/ERK and p38 and degradation of phosphorylated I κ B proteins, all of which are involved in proliferation-differentiation and stress responses of lymphocytes following antigen stimulation (9); (vi) decreased proliferation of peripheral blood mononuclear cells to recall antigen, with concomitant lower expression of the costimulatory receptor CD28 and production of beta chemokines (9); (vii) decreased delayed-type hypersensitivity responses to purified protein derivative (PPD) (10); and (viii) increased levels of lymphocytes expressing cytotoxic T-lymphocyte-associated antigen 4, a negative regulator of T-cell responses (10). Some of these findings have been reported also for populations from other developing countries in Africa and Southeast Asia (13, 26). This clearly indicates that these broad immune dysregulations are representative of a general phenomenon present in populations living in the developing countries.

We have suggested that these broad immune dysregulations are mainly a consequence of helminthic infections (5, 6, 8, 27). This was based largely on the high prevalence of helminthic infections seen in the ETH (35), on the well-known TH2-promoting effect of helminthic infections (37), and on the major observation that most of these immune disturbances in the ETH returned to normal following the eradication of the

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helminthic infections (4, 27). However, several other bacterial, parasitic, or viral infections, such as malaria, tuberculosis, *Leishmania*, hepatitis, and herpes, which are highly endemic in many developing countries, probably contribute to such an unbalanced immune background.

Previous studies have shown that helminthic infections jeopardize the host's ability to generate protective immunity to HIV-1 and other infections, such as *Mycobacterium tuberculosis* (reviewed in references 32 and 43): (i) *Schistosoma*-infected mice with a dominant TH2 immune profile have a TH2-skewed immune response to HIV envelope antigens, which is accompanied by down-regulation of TH1 cytokines and an impaired CTL (TH1) response; (ii) the cytokine response to mycobacterial antigens can be modulated by helminth preinduction of a TH2 response; (iii) selective inhibition of T-cell subsets is evidenced in filariasis, in which T cells show antigen-specific anergy while antibody responses remain intact; and (iv) humans infected with *Schistosoma mansoni* have an impaired tetanus toxoid TH1 response (42). Others have also found that elimination/or reduction in intestinal worms following treatment resulted in a significant improvement in T-cell proliferation and in gamma interferon production by peripheral blood mononuclear cells stimulated with PPD. Moreover, vaccination with *Mycobacterium bovis* BCG (bacillus Calmette-Guérin) significantly improved PPD-specific immune responses in individuals treated with helminth drugs but not in those given placebo helminth treatment (21).

It is important to point out that helminthic infections are common in vast regions of the world, especially in the developing countries, and by the most conservative estimates affect over a quarter of the world's population (~1.5 billion people!) (15). These are chronic, debilitating parasitic diseases which succeed in evading the human immune response in ways that are not completely understood (2), inducing long-lasting chronic infections. In developing countries, in which ~70% of the global population live, a child born in an area where intestinal nematodes are endemic is expected to harbor worms for most of his or her life (2).

The efficacy of candidate HIV-1-protective vaccines will have to be tested in human field trials that can take place only in Africa and Asia, in areas where a high incidence of HIV infections still occurs. However, considering all of the evidence described above, potentially good vaccines may fail in such clinical trials if examined in the immune scenario presently existing in the developing world. It is quite clear that the host immune background in developing countries is biased towards a TH2 profile and that most individuals are in a chronic immune activation state. Our findings that signal transduction in such individuals is impaired and that their immune cells can respond poorly to stimuli, such as to PPD, suggest that their capacity to elicit an immune response following vaccination will be heavily encumbered. The failure of BCG vaccination in Africa and Asia to confer protective immunity to tuberculosis may indeed reflect this effect. It therefore becomes absolutely essential to take this major issue of the host background immunity into consideration for any protective vaccine development.

It is clear that eradication of helminths will enhance the capacity of the host to mount more efficient cellular immune responses following immunological challenges. However, sev-

eral key questions still remain to be answered in the context of development of HIV vaccines. For example, what are the kinetics of the changes of the immune profile following eradication of helminth infection and the conditions necessary for them to persist? Would eradication of the helminth infections by itself be enough to allow for effective immunization? Would helminth eradication bring back the immune profile to a TH0 profile or allow easier manipulation toward a TH1 profile? Is eradication of the helminths essential, or can the preexisting pronounced TH2 background be shifted to a TH0 or TH1 background prior to vaccination by other means, such as by adjuvants, and thus allow for the generation of cellular immunity by HIV vaccines?

The use of TH1-inducing adjuvants, such as oligonucleotides containing CpG motifs, may be essential for HIV vaccines to be effective in areas where helminths are endemic. To study this question, we have recently demonstrated that intradermal immunization of *Schistosoma*-infected mice, with a preexistent dominant TH2 immune background, with plasmid DNA encoding β -galactosidase induced a strong TH1 anti- β -galactosidase response, as opposed to immunization with β -galactosidase alone (3). Importantly, the established protective TH2 immune response to schistosomes was not disrupted. Furthermore, we found that the use of oligodeoxynucleotides containing CpG motifs as adjuvants could overcome the TH2 bias present in *Schistosoma*-infected mice so as to generate HIV-specific TH1-type immune responses following immunization with HIV antigens. Eradication or reduction of *Schistosoma* in these mice further enhanced the generation of anti-HIV-1 immune responses (M. Ayash-Rashkovsky et al., submitted for publication).

In conclusion, taking these findings together, we believe that the preexisting immune profile found in African and other populations should be taken into serious consideration during the development and testing of potential HIV vaccines. Furthermore, it may be that a prerequisite for effective vaccination against HIV in developing countries, especially in Africa and Southeast Asia, is the eradication of helminthic infections, which have a major impact on the immune profile of the host. Eradicating the helminths in this context is feasible and relatively inexpensive. At the least, the possible impact of helminth presence and eradication on the success of candidate HIV vaccines should be investigated prior to and during all future vaccine trials. In addition, other modes of immunomodulation and immune intervention should be explored so as to overcome the possible disturbed immune profile of the host and ensure the generation of an optimal protective immune response by future HIV vaccines.

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