

The Th1–Th2 hypothesis of HIV infection: new insights

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In their earlier, much quoted, viewpoint article, Mario Clerici and Gene Shearer examined the role of T helper 1 (Th1)- and Th2-type responses in immune dysregulation associated with human immunodeficiency virus (HIV) infection. In this article, they consider the complications of a Th1–Th2 model raised by the nomenclature, discuss the issue of cytokine production by non-T cells, and compare data obtained from T-cell clones with heterogeneous populations of leukocytes from patients. They define Th-cell responses and cytokine profiles as 'type 1' and 'type 2', and re-emphasize the importance of strong cellular immune responses, along with the cytokines that augment and maintain such responses, in protective immunity against HIV infection and AIDS progression. Finally, they present a model of activation-induced, cytokine-modulated, programmed cell death as a major factor in the pathogenesis of HIV infection and AIDS.

In the March 1993 issue of *Immunology Today*, we suggested that the immune dysregulation observed in individuals infected with human immunodeficiency virus (HIV) during progression towards AIDS could be accounted for by a shift from a T helper 1 (Th1)- to a Th2-type cytokine profile¹. Based on *in vitro* measurements of cytokines produced by antigen- and mitogen-stimulated peripheral blood mononuclear cells (PBMCs) of HIV-infected (HIV⁺) individuals during progression towards AIDS (Refs 2–4), we proposed that a dominant Th1-type cytokine profile would be more protective against disease progression than a dominant Th2-type cytokine profile. It has been shown that HIV-specific cellular immune responses, but not humoral immune responses, can be detected in cohorts of individuals multiply exposed to HIV, many of whom do not appear to be infected^{5–8}. Thus, we further suggested that a dominant Th1-type cytokine profile, along with the strong cellular immune response it promotes, would also be more protective against initial HIV infection than a dominant Th2-type cytokine profile and its associated antibody responses¹. It was our intention to make the model provocative enough to initiate debate^{9,10} and to generate experimentation, with the ultimate hope of exploring possible immunological approaches to combating AIDS. Here, we expand our perspectives on the model by considering problems of nomenclature, the issue of cytokine production by non-T cells, and a recently proposed mechanism by which loss of Th1-like function could occur.

Considerations and complexities

In mice, the Th1–Th2 model of immune regulation is complex and has not yet been fully elucidated; in humans, the problem may be even more complex^{11,12}. This has resulted in several problems, particularly concerning nomenclature. For example, the terms originally used to classify Th-cell clones, Th0, Th1 and Th2, can be con-

fusing when applied to more-physiological polyclonal Th-cell responses. The use of these terms to describe cytokine profiles ignores the fact that important human immunoregulatory cytokines are also produced by non-T cells, including monocytes/macrophages, natural killer (NK) cells and B cells. Thus, by definition, the Th1/Th2 nomenclature excludes cytokines produced by accessory cells, the function of which can be perturbed by their infection with HIV (Ref. 13). For instance, interleukin 10 (IL-10) is produced by monocytes/macrophages, as well as by Th2 clones¹². Consequently, having previously employed terms such as Th1-type/Th2-type or Th1-like/Th2-like to describe the helper cells that primarily enhance cellular and humoral responses respectively^{1–14}, we now prefer to use 'type 1' and 'type 2' terminology in a similar manner to that used to describe the *in situ* cytokine patterns characteristic of leprosy¹⁵. Thus, using our definition, IL-10 is considered a type 2 cytokine on the basis of the responses it modulates rather than on the cell type that produces it.

We define a type 1 response as a strong cellular immune response with normal or increased levels of IL-2, IL-12 and interferon γ (IFN- γ); and a type 2 response as a reduced or undetectable cellular response accompanied by an increase in one or more B-cell activities (for example, hypergammaglobulinemia, autoantibody production or hyper-IgE) and an increase in IL-4, IL-5, IL-6, IL-10 and/or IL-13 (Refs 16,17). In addition, we define type 1 cytokines, including IL-2, IL-12 and IFN- γ , as those that primarily stimulate cell-mediated immunity (CMI) [e.g. those that stimulate the activity of cytotoxic T lymphocytes (CTLs) and NK cells]; and type 2 cytokines, including IL-4, IL-5, IL-6 and IL-10, as those that primarily induce B-cell differentiation and expansion (Fig. 1).

The Th1/Th2 nomenclature has been complicated even more by the recent finding that type 2 cytokines

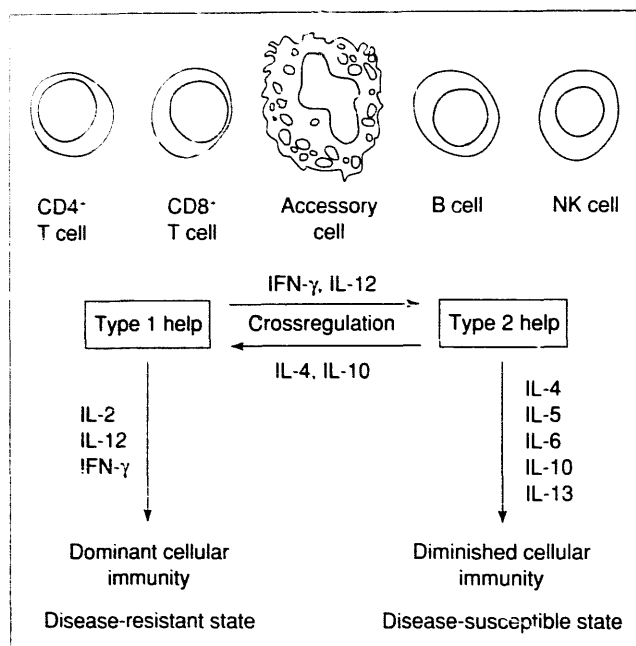


Fig. 1. Definition of type 1 and type 2 responses and cytokine profiles, and the effect suggested to result from such T-cell help. Type 1 and type 2 cytokines are produced by multiple different cell types, including CD4⁺ T helper (Th) cells, CD8⁺ T cells, accessory cells, B cells and natural killer (NK) cells, as shown in the diagram. Abbreviations: IFN- γ , interferon γ ; IL, interleukin.

can be produced by CD8⁺ T cells in a subset of AIDS patients¹², which may be similar to that reported for immune dysregulation in leprosy¹⁵. We therefore prefer to define immunoregulatory cytokines on the basis of function (i.e. type 1/type 2) rather than on the cell type that produces them (i.e. Th1/Th2). This is particularly important since: (1) a cell marker that unequivocally distinguishes Th1 from Th2 cells is not yet available; and (2) some of the Th1 and Th2 cytokines have been shown to be produced by non-CD4⁺ cells and by non-T cells.

The fact that type 1 and type 2 cytokines can be produced by non-T cells presents potential problems that go beyond nomenclature. For instance, the cloning of Th cells is likely to be affected, since results may be biased by the loss (during the cloning process) of important, non-T, accessory cells that produce cytokines with immunoregulatory properties. Thus, human monocytes/macrophages and B lymphocytes are major producers of IL-10 (Ref. 18) and IL-12 (Ref. 19), and NK cells produce IFN- γ (Ref. 20). Furthermore, current techniques involve the selection and expansion of cells in relatively high concentrations of IL-2, and this may result in the selection of populations of T cells. Moreover, it was recently reported that feeder cells required for generation of human Th clones can produce IL-12, which could favor a Th2 to Th1 shift, even at the clonal level^{10d}. Finally, the study of cloned T cells only analyses the cytokines produced by these clones and is limited to autocrine regulation. By contrast, the investigation of PBMCs analyses the effects of cytokines produced by multiple cell types on Th-cell function, and includes both autocrine and paracrine regulation. Thus, T-cell clones may be an oversimplification of the situation that occurs *in vivo*.

Consistencies

Despite the potential caveats of cloning Th cells described above, two groups have recently reported the selective outgrowth of Th2 (Ref. 21) or Th0/2 (Ref. 12) clones, which produce type 2 cytokines, from PBMCs of HIV-infected individuals. A longitudinal follow-up in one of the studies²¹ suggested an increase in the number of Th2 clones with disease progression towards AIDS. Indeed, HIV appears to infect and replicate in Th2 clones more efficiently than in Th1 clones^{12,22}. Furthermore, Th1 but not Th2 clones protect against HIV infection *in vitro*²², and this effect is not major histocompatibility complex (MHC) restricted, as autologous and HLA-mismatched cells are both protected²². In this context, it is noteworthy that type 2 cytokines, particularly IL-10 (Ref. 23), can interfere with the activity of a soluble factor, produced by CD8⁺ T cells, that blocks HIV infection *in vitro*²⁴.

Other recent studies (Refs 25–31; D. Brugnani, R. Cattaneo, M.T. Franzini *et al.*, unpublished) have verified our findings that type 1 cytokines are decreased and type 2 cytokines are increased in HIV⁺ individuals in the progression towards AIDS. Some studies have reported an increase in type 2 cytokines without a concomitant decrease in type 1 cytokines²⁹. One group has not observed the cytokine changes that would suggest a loss of type 1 function and/or an increase in type 2 function³². Such inconsistencies observed between laboratories could be due to differences in the experimental design and the material tested, such as: (1) use of cytokine mRNA *versus* protein; (2) study of constitutive *versus* induced expression or production; (3) use of different stimuli in the induction studies; (4) sampling of different tissues; (5) the differential sensitivities of different cytokine assays; (6) differences in the total number of HIV⁺ individuals studied; and (7) sampling of HIV⁺ individuals at different stages of disease progression. For example, concerning the latter possibility, we have observed that, among asymptomatic HIV⁺ individuals, only the subset distinguished by selective loss of self-MHC-restricted Th function exhibited a marked increase in the production of IL-4 (Ref. 3).

Redefining the model

Although phenotypic markers that distinguish Th1 and Th2 cells have not been identified, it was recently found that CD4⁺CD7⁺ cells mainly produce type 1 cytokines, whereas CD4⁺CD7⁻ cells mainly produce type 2 cytokines^{33,34}. Interestingly, in HIV⁺ patients, the number of CD4⁺CD7⁻ cells increases and the number of CD4⁺CD7⁺ cells decreases in parallel with progression to AIDS (Refs 33,34). The finding that defective type 1 function can be restored in PBMCs from HIV⁺ individuals by adding type 1 cytokines (e.g. IL-12) (Ref. 35) and/or antibodies to type 2 cytokines (e.g. anti-IL-4 and anti-IL-10) (Refs 3,4), and that HIV⁺ CTL function can be restored *in vitro* by the addition of IL-2 (Ref. 36), suggests an endogenous imbalance in the immunoregulatory cytokine network.

Redefining the Th1–Th2 model in terms of type 1 and type 2 cytokine profiles could also be relevant for other diseases. Leprosy is an example of a human condition with clear-cut Th1 (tuberculoid) and Th2 (lepromatous)

phases¹⁵. However, three intermediate stages (borderline tuberculoid, borderline, borderline lepromatous) have also been described³⁷. These three stages probably do not conform to the extremes of Th1/Th2 clones, but nevertheless are part of a slowly developing but dynamic condition. A similar comparison of the more extreme forms of tuberculosis might also be made. Tuberculosis pleuritis is characterized by a positive tuberculin skin test and resolution of the disease, whereas the advanced stages of pulmonary tuberculosis are characterized by a negative skin test and progressive clinical decline³⁸⁻⁴⁰. Intermediate stages may also exist in which the pattern is not so clearly defined.

Thus, as immunoregulatory cytokines become better understood for their contribution to disease states, and as cytokine-based therapy becomes more common, it may be important to describe and define the effects of cytokine-induced dysregulation in terms that are less stringent than those suggested by Th1/Th2 clones. Figure 2 illustrates the possibility that *in vitro* immunoregulatory cytokine profiles may not always conform to the extreme examples observed in Th1 and Th2 clones. A more frequent situation may occur in which Th cells are not irreversibly committed to one or other pathway, but could reside somewhere on the slope shown in Fig. 2. If this model is correct, it may suggest that immunoregulatory cytokine therapy could be effective if intervention is initiated sufficiently early in disease progression. This model also predicts that HIV-infected long-term non-progressors would cluster towards the type 1 side of the figure, whereas rapid progressors would be skewed more towards a dominant type 2 cytokine profile (see below).

It is generally considered that, for immunity against viruses, antibodies are protective against initial infection, whereas CTL responses are protective by controlling established infection. However, it has been noted that HIV infection can occur by the transfer of cells that carry HIV proviral DNA, and that antibodies would be ineffective against such infection^{14,41,42}. Thus, the more traditional dogma of protective immunity may not be as applicable for HIV infection, or for viruses that integrate into the genome of the host leukocytes, as for other viral infections.

The original Th1-Th2 model proposed that a type 1 cytokine profile, and the subsequent strong cellular immune response, is important in protection against HIV infection¹. It has been argued that such an immune profile is not protective against initial HIV infection because individuals who are able to elicit a strong cellular response to HIV nevertheless become infected⁴³. However, this argument may not be valid, because protection against infection of an unimmunized individual may be dependent on the dose of virus and route of infection. Thus, we suggest that exposure of an unprimed immune system to a relatively high dose of virus is likely to provoke HIV infection, and seroconversion, despite the presence of strong cellular immune potential. By contrast, exposure to a relatively low dose of HIV can result in priming of the cellular arm of the immune system, followed by subsequent control or elimination of infection after challenge with higher doses of HIV (Ref. 14). For instance, it is known that

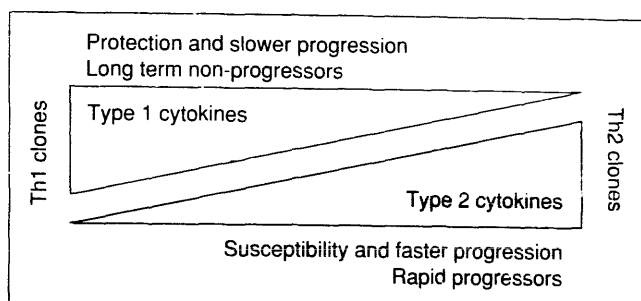


Fig. 2. Diagram illustrating the interplay between protective and susceptible type 1 and type 2 cytokines, and the immune responses they elicit. The extreme cases illustrated by the Th1 and Th2 clones at either ends of the diagram are unlikely to occur frequently in patient populations. The relative positions of human immunodeficiency virus (HIV)-infected long-term non-progressors and rapid progressors are shown on the scale.

low-dose immunization of uninfected volunteers with a candidate recombinant gp160 AIDS vaccine results in priming for strong Th-cell responses without eliciting seroconversion⁴⁴. Further support for this hypothesis is provided by the findings that: (1) a high proportion of multiply exposed, HIV-seronegative individuals remain virus free, as shown using the polymerase chain reaction (PCR), but exhibit strong HIV-specific Th-cell activity, including helper cell responses^{5-8,45-47} and MHC class I-restricted CD8⁺ T-cell-mediated effector cell responses (Refs 48,49; L.A. Pinto and G.M. Shearer, unpublished); and (2) macaque monkeys exposed to 'sub-infectious' doses of simian immunodeficiency virus (SIV) exhibit potent SIV-specific cellular, but not humoral, immune responses^{50,51} and are resistant to challenge with infectious doses of SIV (Ref. 51). Furthermore, approximately 10% of the multiply exposed, Th-cell-reactive, seronegative individuals are positive for proviral DNA (but not for proviral RNA) by PCR (M. Clerici *et al.*, unpublished).

Successful priming against HIV, and possibly against subsequent challenge, may depend on the individual exhibiting a strong type 1 cytokine profile. Thus, it is possible that individuals with a low type 1 or a dominant type 2 cytokine profile will be susceptible to infection following exposure to lower doses of HIV. Other infections, such as with helminth parasites⁵²⁻⁵⁴, certain mycoplasma and mycobacteria strains⁵⁵⁻⁶⁰, or sexually transmitted diseases such as syphilis⁶¹, could reverse the balance from type 1 to type 2 cytokines. Such infections could therefore render an individual more susceptible to HIV infection and could be considered as cofactors. If correct, such cofactors may contribute to the higher incidence of seroconversion and more-rapid progression to AIDS in those areas of the world in which parasitic infections that induce type 2 profiles are endemic^{62,63}. Hyper-IgE, driven by an increase in the production of IL-4, has been reported in HIV⁺ patients⁶⁴, resulting in a higher incidence of atopic diseases and allergic reactions to drugs^{65,66}. Likewise, hyper-eosinophilia has been observed⁶⁷ secondary to increased production of IL-5. Several laboratories have recently shown that the progression to AIDS of HIV⁺ atopic patients with hyper-IgE is significantly accelerated^{12,68,69}. Other genetic cofactors could also be involved. It was reported that the HLA-A1/B8/DR3 haplotype is susceptible to rapid progression to AIDS (Ref. 70).

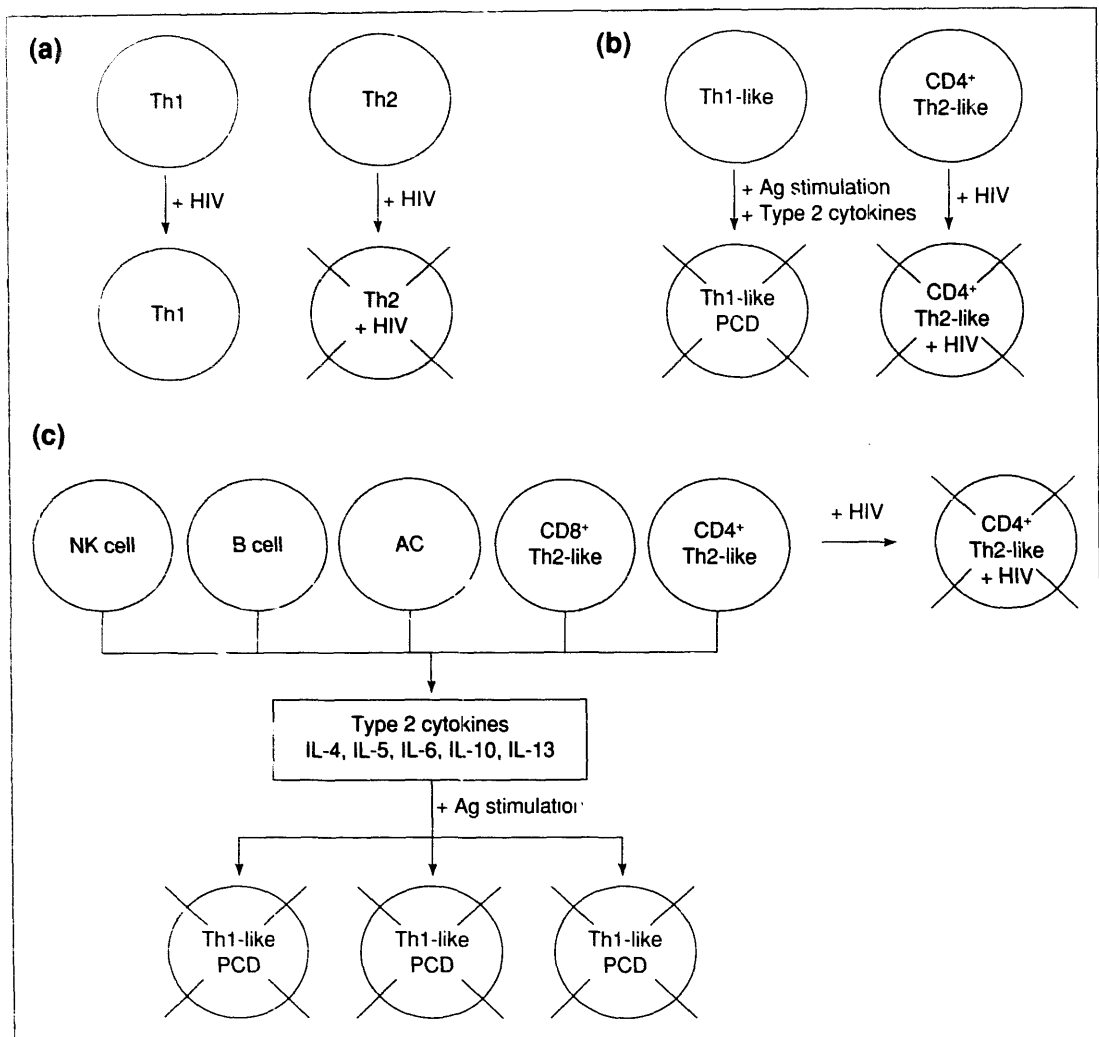


Fig. 3. Models of programmed cell death (PCD) and human immunodeficiency virus (HIV)-induced T helper (Th)-cell depletion. (a) Selective HIV-induced infection and destruction of CD4⁺ Th2 clones. (b) In vitro T-cell activation and PCD induced by type 2 cytokines of Th1-like cells, and HIV-induced destruction of Th2-like cells. (c) In vivo T-cell activation and PCD induced by type 2 cytokines of Th1-like cells, and HIV-induced destruction of Th2-like cells. In model (c), type 2 cytokines are produced by natural killer (NK) cells, B cells, accessory cells (AC), CD8⁺ Th2-like cells and CD4⁺ Th2-like cells. PCD following stimulation with antigen (Ag) is induced directly by type 2 cytokines, or indirectly by reducing the concentration of type 1 cytokines via cytokine cross-regulation. In model (a), the type 1 and type 2 cytokines produced by Th clones act exclusively in an autocrine way. By contrast, the type 1 and type 2 cytokines generated in vitro by peripheral blood mononuclear cells (PBMCs) in model (b) and in vivo in model (c) exert autocrine and paracrine effects. Th2-like, but not Th1-like, cells are protected from PCD due to the differential expression of the Fas ligand². In all three models, shading indicates Th2 or Th2-like cells.

It was subsequently suggested that individuals who express this haplotype exhibit a less dominant type 1 cytokine profile¹.

New insights for the model

The progressive loss of type 1 cytokines is predictive of three clinically relevant parameters: (1) a decline in CD4⁺ T-cell count²; (2) time to AIDS diagnosis³; and (3) time to death³. We have recently begun to investigate whether these phenomena are related. Several groups have reported that PBMCs from HIV⁺ individuals undergo programmed cell death (PCD), either spontaneously or following *in vitro* stimulation⁴⁻⁶. Using PBMCs from HIV⁺ individuals, we have found that type 1 cytokines (IL-2, IL-12 and IFN- γ) can prevent such activation-induced PCD *in vitro*, whereas

type 2 cytokines (IL-4 and IL-10) increase PCD (Ref. 77). Conversely, antibodies to type 2 cytokines protect against PCD, whereas antibodies to type 1 cytokines increase PCD (Ref. 77). This latter finding suggests that endogenously produced cytokines can influence the susceptibility of HIV⁺ PBMCs to PCD. Therefore, we suggest that the complex alterations observed in the profile of immunoregulatory cytokines in HIV⁺ individuals, characterized by a reduction in type 1 cytokines and an increase in type 2 cytokines, play a significant role in progression to AIDS, and can potentially account for the decline in CD4⁺ Th-cell count.

The models shown in Fig. 3 illustrate the different mechanisms that we suggest for killing of Th2 clones (Fig. 3a) and Th1-like and Th2-like cells *in vitro* (Fig. 3b), and of Th1-like and Th2-like cells *in vivo* (Fig. 3c).

These models incorporate the recent findings of Vyakarnam *et al.*²² and Maggi *et al.*¹², who reported that Th2, but not Th1, clones are susceptible to HIV infection. These findings raise the possibility that Th2 clones and Th2-like cells are more susceptible to viral-induced killing than Th1 clones and Th1-like cells. Th1-like cells are induced to undergo PCD by activation in a dominant type 2, rather than type 1, cytokine environment (Fig. 3b), but are protected from PCD by the type 1 cytokines IL-2, IFN- γ and IL-12. As shown in Fig. 3c, Th2-like cells, accessory cells, CD8⁻ cells, B cells and NK cells, which all produce type 2 cytokines, induce a dominant type 2, rather than type 1, cytokine imbalance that results in PCD-induced death of activated Th1-like cells. Thus, we suggest that activated Th1-like cells will be preferentially killed by type 2 cytokine-induced PCD, whereas Th2-like cells may be destroyed by preferential HIV infection. Since the percentage of HIV-infected lymphocytes is small, and Th1-like lymphocytes can be killed by PCD upon release of type 2 cytokines, many more Th1-like cells would die relative to the infection-induced death of Th2-like cells. This would lead to a progressive loss in the proportion of Th1-like cells, and a progressive enrichment of Th2-like cells. In addition, it has recently been suggested that the interaction between Fas and its ligand will result in PCD of T-cell lines *in vitro*⁷⁸⁻⁸⁰. Th1 clones express high levels of Fas ligand, whereas Th2 clones express low levels⁸¹, and it has been proposed that such differential expression of Fas ligand correlates with the relative abilities of Th1 and Th2 cells to undergo PCD, such that PCD is observed in Th1 but not in Th2 clones⁸¹.

Several predictions can be made from this model and these have been listed in Box 1. One outcome of the progressive depletion of Th1-like cells could be an increase in the concentration of type 2 cytokines. This would create a self-amplifying loop in which Th0-like cells are preferentially driven towards the Th2-like rather than the Th1-like pathway of differentiation^{84,85}. The concept of a self-amplifying type 2 loop is further supported by the recent findings of Erard *et al.*⁸⁶ and Le Gros *et al.*⁸⁷ that CD8⁺ T cells activated in the presence of IL-4 develop into non-cytolytic CD8⁻ and cytolytic CD8⁺ subsets, which themselves produce IL-4, IL-5 and IL-10, but not IFN- γ .

Therapy

Cytokine-based therapy that replenishes type 1 cytokines and enhances cellular immune responses should be considered as an approach for management of HIV disease. It may be necessary to use such therapy in conjunction with anti-retroviral drugs because of the potential risks involved. This therapy could involve type 1 cytokines^{32,33}, and/or antibodies to type 2 cytokines^{3,4,88}, and would be aimed at restoring cellular immune responses and the CD4⁺ T-cell count, possibly *via* a reduction in PCD. IL-12 might also be considered as an adjuvant that would selectively enhance type 1 immune responses^{35,89}. It may be significant that preliminary data from a protocol involving IL-2 has resulted in a substantial increase in the CD4⁺ T-cell count in some patients⁹⁰. If type 1 cytokine therapy results in

Box 1. Predictions of a Th1-Th2 model for HIV infection

- (1) A relatively small proportion of CD4⁺ T helper (Th) cells are infected by human immunodeficiency virus (HIV), (Refs 82,83) and these are mainly, if not exclusively, Th2-like cells¹².
- (2) Depletion of CD4⁺ Th1-like cells results from dominant type 2 cytokine-induced programmed cell death (PCD). This PCD results in preferential depletion of Th1-like cells, and the selective loss of cellular immune responses (J.C. Amiesen, unpublished).
- (3) T-cell clones are different from primary cultures of leukocytes, and from T cells *in vivo*, with respect to their susceptibility to cytokine-mediated PCD.
- (4) As the proportion of Th1-like and Th2-like cells changes in favor of the Th2 viral-permissive side, an increase in viral load will occur.
- (5) Th1 clones and Th1-like cells will be susceptible to productive HIV infection in the presence of type 2 cytokines and/or antibodies against type 1 cytokines.

appreciable adverse side-effects, it may be worth considering therapy based on humanized antibodies against type 2 cytokines⁸⁸. Combination therapy involving type 1 cytokines, along with antibodies against type 2 cytokines, might then be the most effective strategy. Alternatively, it may be possible to provide immunological stimuli that would activate endogenous type 1 cytokine production⁹¹. Such an approach might also have less-severe side-effects.

Another possible approach for therapy is suggested by the findings that: (1) cortisol and glucocorticoids impede T-cell proliferation by inhibiting IFN- γ and IL-2 production⁹²; (2) glucocorticoids enhance IL-4 production and B-cell differentiation⁹²; (3) dehydroepiandrosterone sulfate (DHEAS) and its derivative dehydroepiandrosterone (DHEA) are physiological antagonists of the immunoregulatory activities of cortisol⁹³; and (4) increased cortisol and decreased DHEA production is characteristic of progression to AIDS (Refs 94-96). It has recently been suggested that such a hormonal imbalance could contribute to the type 1 to type 2 cytokine shift observed in AIDS progression (Refs 97-99; D.H. Katz, unpublished). Thus, it may be possible to modulate cytokine production and slow the progression to AIDS by hormone-based therapy.

Concluding remarks

The primary focus of the management of HIV infection and AIDS should be to achieve and maintain a strong HIV-specific cellular response, including, but not limited to, MHC class I-restricted CTL responses. Other, non-HIV-specific cellular responses should be evaluated to assess the type 1/type 2 profile of cytokine production. These include antigen- and mitogen-stimulated *in vitro* proliferation and cytokine production, assessment of NK and CTL activity, and *in vivo* evaluation of delayed-type skin reaction to recall antigens, including HIV antigens. We define the cytokines that modulate such an immunological condition as type 1. These type 1 cytokines are also likely to provide help for certain classes of antibodies, and it would be

interesting to determine whether these antibodies have protective properties. We do not suggest that antibody production in HIV⁻ patients is necessarily and implicitly damaging, although certain antibodies may have this negative effect^{100,101}, as shown by the observation that seropositivity is ultimately indicative of the inability of the immune response to control HIV replication. It remains to be established whether it will be possible to achieve the 'best of both worlds': optimal, protective, cellular and humoral immune responses¹⁴.

A prediction of the model described here is that a type 1 cytokine profile would be observed in HIV⁻ long-term non-progressors, whereas a type 2 cytokine profile would be characteristic of progressive disease (Fig. 2). Recent studies have observed these different cytokine patterns in multiple cohorts of seropositive patients who exhibit different rates of disease progression (Refs 102,103; M. Clerici *et al.*, unpublished).

The issues presented above will need to be considered in the context of designing effective preventive AIDS vaccines. Critical decisions are required concerning the engineering of the vaccine itself, route of administration, dose of vaccine, adjuvant to be used, the immune response to be evoked and the population of individuals to be tested. Other factors may also need to be considered, including: (1) the type 1/type 2 cytokine profiles before and after immunization; (2) other infections that could alter the cytokine profiles before, and perhaps after, immunization (i.e. possible cofactors); and (3) whether the population to be vaccinated has been previously exposed to HIV and may be primed for cellular but not humoral reactivity prior to vaccination⁶⁻⁹. By modulating these variables, we may be able to teach the immune system to elicit potentially protective responses against HIV infection and/or AIDS progression.

Finally, the debate of our model appears to be focused on whether the cells that produce type 2 immunoregulatory cytokines should be called 'Th2', 'Th2-like' or 'Th0/2' (Refs 12,29,32). However, we believe that the more important points of the model are: (1) that a strong cellular immune response, and the type 1 cytokines that augment this component of the immune system, are protective against HIV infection and progression to AIDS; and (2) that a shift away from the dominant production of immune-protective type 1 cytokines to a dominant type 2 cytokine profile is observed in the progression to AIDS (Refs 12,25-31).

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