A $T_H1 \rightarrow T_H2$ switch is a critical step in the etiology of HIV infection

Mario Clerici and Gene M. Shearer

This viewpoint proposes that an imbalance in the T_H1-type and T_H2-type responses contributes to the immune dysregulation associated with HIV infection, and that resistance to HIV infection and/or progression to AIDS is dependent on a $T_H1 > T_H2$ dominance. This hypothesis is based on the authors' findings that: (1) progression to AIDS is characterized by loss of IL-2- and IFN-γ production concomitant with increases in IL-4 and IL-10; and (2) many seronegative, HIV-exposed individuals generate strong T_H1-type responses to HIV antigens.

It is generally considered that the immune system is at a serious disadvantage in resisting infection by the human immunodeficiency virus type 1 (HIV). Such pessimism is understandable given that: (1) HIV infection results in a profound depletion of $CD4^+$ T helper (T_H) cells[1]; (2) HIV is unique in using CD4 in its infective process[2,3]; and (3) the virus has a high rate of mutation[1], which has frustrated and discouraged attempts to develop an AIDS vaccine.

From an immunological perspective, certain events that occur following HIV infection are paradoxical. For example, $CD4^+$ cell numbers (CD4 count) and helper function, assessed by T-cell proliferation and interleukin 2 (IL-2) production, decline, although B-cell activity increases[1,4,5], and helper function declines even when CD4 counts exceed 500/μl[6]. Researchers have concentrated on studies of HIV-seropositive individuals (HIV^+), most of whom develop symptoms of the acquired immunedeficiency syndrome (AIDS). However, a large number of individuals have been exposed to HIV (many of them multiple times) without becoming HIV^+ and without developing the symptoms of AIDS.

Our laboratory has extensively studied the proliferation of and the IL-2 production by peripheral blood mononuclear cells (PBMCs) of asymptomatic, HIV-seropositive (HIV^+) individuals in response to recall antigens such as influenza A virus, tetanus toxoid and HIV synthetic peptides, as well as to HLA alloantigens (allo-MHC), and phytohemagglutinin (PHA)[6–9]. There is a sequential and progressive loss of T_H function such that the T_H cell response to recall antigens is the first to be lost, followed by loss of T_H function to allo-major histocompatibility complex (allo-MHC), and finally by loss of reactivity to PHA[6,7]. Analysis of more than 600 HIV^+ asymptomatic individuals who were clinically indistinguishable from noninfected individuals indicated that PBMCs from 34% responded to all three stimuli (designated +/+/+); 40% were selectively unresponsive to recall antigens, but responded to allo-MHC and PHA (designated –/+/+); 11% responded to PHA only (designated –/–/+); and 15% were unresponsive to all three stimuli (–/–/–). These defects are associated with, or predictive of a number of AIDS-related events such that individuals with –/+/+, –/–/+ or –/–/– profiles exhibit a more rapid decline in $CD4^+$ T-cell numbers[10]; a higher incidence of bacterial and opportunistic infections (in pediatric HIV^+ patients)[11]; are more likely to progress rapidly to AIDS (authors' unpublished observations), and have higher levels of β_2 microglobulin[12] in the cerebrospinal fluid than individuals with the +/+/+ profile. Thus, the sequential loss of T_H function is in the direction (+/+/+)→(–/+/+)→(–/–/+)→(–/–/–).

Although the incidence of spontaneous reversals in these T_H patterns is low, improvement in T_H function which is independent of $CD4^+$ T-cell number can be detected in 50–75% of patients who are on AIDS therapeutic protocols[13]. Furthermore, improved T_H function correlated with infection-free follow-up periods, whereas changes in $CD4^+$ T-cell number did not[13].

On the basis of the findings summarized above, it is clear that loss (and recovery) of T_H function can occur in HIV^+ individuals and AIDS patients independently of the $CD4^+$ T-cell count. The mechanism(s) responsible for this phenomenon has not been elucidated, but possibilities that have been considered include: (1) the selective loss of memory cells[14,15], (2) a defect in antigen-presenting cells (APC)[16], (3) the production of antibodies that block T-cell–APC interactions[17], (4) the production of immunosuppressive products of HIV such as the protein gp120 (Ref. 18) and Tat (Ref. 19), (5) the induction of suppressor cells and factors[20–22], and (6) the elaboration of cytokines that exhibit immunoregulatory properties[23–25]. Because immunodysregulation in the progression to AIDS involves loss of helper function (as assessed by proliferation and IL-2 production), B-cell activation and hypergammaglobulinemia, we consider immunoregulatory cytokines as a useful marker of disease progression.

T_H1 and T_H2 cells

Clones of mouse T_H cells produce distinct profiles of cytokines that modulate the effector arm of the immune system[26,27]. T_H1 clones produce gamma-interferon (IFN-γ) and IL-2, and promote cell-mediated

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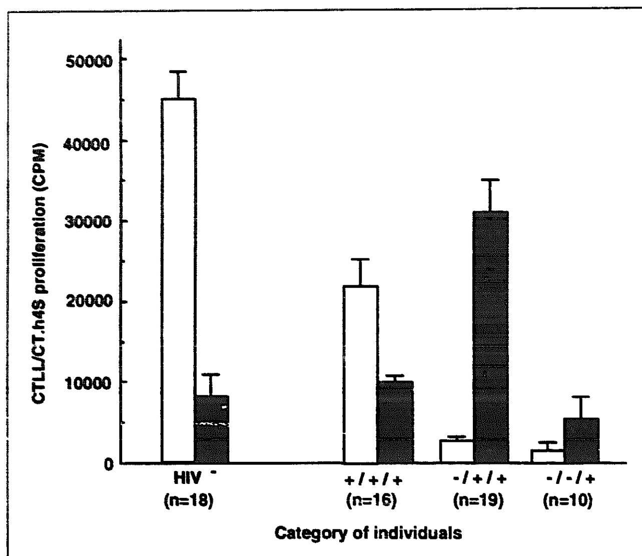

Fig. 1. *Mean counts per minute (CPM) for IL-2 production stimulated by recall antigen (□) and PHA-stimulated IL-4 production (■) from four groups of individuals including: 18 HIV⁻ control donors; 16 HIV⁺ individuals whose PBL generated high IL-2 but low IL-4; 19 HIV⁺ individuals whose PBL generated low IL-2 but high IL-4; and 10 HIV⁺ individuals whose PBL generated both low IL-2 and IL-4. The mean CPM obtained from the 1:2 dilutions of the supernatants from influenza virus-stimulated IL-2 and PHA-stimulated IL-4 production by each individual are shown with standard errors. IL-2 production was assessed using the IL-2-dependent CTLL cell line, and IL-4 production was detected using the CT.h4S cell line (kind gift of Dr W.E. Paul).*

effector responses; whereas T_H2 clones produce IL-4, IL-5, IL-6 and IL-10, cytokines which influence B-cell development and can augment humoral responses. T_H1 and T_H2 cells may represent the ends of a spectrum of cytokine patterns, so that categorizing only two types of responses may be an oversimplification[27-30]. Cytokines produced by one type of T_H clone can downregulate the other type of T_H clone[28,29]. IFN-γ can downregulate T_H2 clones and IL-10 can downregulate T_H1 clones. Clones of T_H1 and T_H2 cells have been recently isolated from humans[31,33], providing opportunities for an analysis of cytokine-mediated regulation of human immunity and diseases.

The findings in HIV⁺ individuals that T-cell proliferation and IL-2 production declines while B-cell activity increases, suggested to us that a $T_H1 \rightarrow T_H2$ switch occurs in the progression to AIDS[23,24]. However, this was difficult to assess as our assay for T_H function was based on the production of IL-2 rather than IFN-γ, which might have been a better indicator of T_H1 function. Thus, despite the fact that an early defect involves the loss of recall antigen-stimulated IL-2 production mediated by memory cells, it was not certain that we were exclusively measuring T_H1 function. Nevertheless, we have recently reported that the selective loss of IL-2 production in response to recall antigens (–/+/+ profile) is correlated with an increase in PHA-stimulated IL-4 production (Fig. 1) (recall antigens do not stimulate detectable IL-4 production)[25,34]. These data are based on the IL-2/IL-4 profiles of more than 100 HIV⁺ individuals, each tested at one point in time. In addition, we recently tested for PHA-stimulated IFN-γ production in an enzyme-linked immunosorbent assay (ELISA) and found that the loss of recall and allo-MHC-stimulated IL-2 production was associated with a concomitant loss of PHA-stimulated IFN-γ. These latter results strongly suggest that we are observing a decline in T_H1 function in the progression from +/+/+ to –/+/+ and –/–/+ (Fig. 2).

If IL-4, a T_H2 cytokine, provides crossregulation by suppressing (directly or indirectly) IL-2 production, it might be possible to reverse the loss of help for recall antigens by stimulating PBMCs from a –/+/+ individual in the presence of anti-IL-4 specific antibody (BL-4P). As predicted, addition of the anti-IL-4 antibody at the initiation of stimulation can restore profileration stimulated by influenza A virus in a proportion of HIV⁺ individuals with a –/+/+ IL-2 profile. These results suggest that cytokine crossregulation is involved in the loss of early T_H function, and raises the possibility of cytokine-based therapies in HIV-infected individuals.

We have begun to follow HIV⁺ individuals longitudinally for IL-2 and IL-4 production, using primary cultures of PBMCs. Initially, there is a time-dependent reciprocal relationship between IL-2 and IL-4 production in HIV infection. However, to our surprise, IL-4 also eventually declined, and this was not accompanied by increases in IL-2. IL-10 may be an important T_H2 crossregulatory cytokine in progression to AIDS, and may be produced in the later stages of HIV infection, when both IL-2 and IL-4 have declined (Fig. 2).

HIV peptide-induced IL-2 production in exposed HIV-seronegative individuals

It has been established that HIV seropositive individuals progress to AIDS. However it is not so well known that thousands of individuals have been exposed to HIV (many of them with multiple exposures) but have not seroconverted. It is possible that the immune system of at least some of these individuals have encountered HIV, and the T_H1 cells of these individuals might therefore produce IL-2 when stimulated *in vitro* with HIV antigens. Because HIV infection is likely to result from the transfer of HIV-infected cells, without an appreciable amount of free virus, cell-mediated immunity could be a more important component of immunity than generation of antibodies in providing immune-protection by destroying HIV-infected cells, thereby limiting, if not preventing, infection. Once host cells are infected, the same mechanism could continue to provide protection as long as the infection does not 'outrun' cellular immunity.

We have collaborated with Dr Jay A. Berzofsky (NCI, Bethesda, MD) in studies of *env*-induced IL-2 production by PBMC from HIV⁻ individuals at risk for infection with HIV. We reported that PBMCs from 6/6 high risk HIV⁻ gay men generated strong IL-2 responses when stimulated with *env*[35,36]. All six were initially seronegative and PCR⁻. Follow-up testing indicated that 4/6 remained T_H *env*-reactive and seronegative for the duration of the study, whereas 2/6 seroconverted and simultaneously became PCR⁺. Additional studies of more than 100 exposed, HIV⁻ individuals indicate that between 39% and 75% of HIV⁻ and PCR⁻ gay men, intravenous drug users, accidental

needlestick health-care workers and newborn infants of HIV+ mothers responded to *env* by IL-2 production (authors' observations). In contrast, 7/167 (5% of presumed unexposed HIV- individuals responded to one or more *env* peptides; of these only 3/167 (2%) responded to more than one *env* peptide.

These findings raise the possibility that an appreciable number of such exposed individuals have encountered HIV, either in the form of non-infectious HIV antigens or as a limited viral infection. By either means, these individuals, including newborns, have become primed to HIV. Because some of them continue to be exposed to HIV by high-risk behaviour, it is probable that they would encounter sufficient HIV to result in seroconversion and the detection of infection by PCR. Nevertheless, many persist in this T_H1-reactive, seronegative state, which raises the possibility of cell-mediated immune-protection. Once host cells have become infected, the same mechanism could continue to provide protection if the infection does not 'outrun' the cell-mediated immune response. Finally, after the immune system has been primed, it should be capable of protecting against a higher intracellular viral load.

The model

Taken together these findings raise the possibility that T_H1-type responses are immunoprotective and can prevent HIV infection and/or progression to AIDS[25]. In contrast, seroconversion and the detection in PBMC of viral nucleic acid by PCR could be correlated with the transition from a predominantly T_H1 state to a T_H2 bias in the response to HIV; the latter state would be more susceptible to infection with HIV and/or progression to AIDS. At present it is not clear whether the *env* IL-2 responses are due to (possibly low level) infection, or whether the individuals from these 'at-risk' groups have all been immunologically exposed to HIV but not infected. Our findings are also consistent with the AIDS cofactor hypothesis. Thus, any immunological stimulus that would induce a $T_H1 \rightarrow T_H2$ switch could serve as an AIDS cofactor. The $T_H1 \rightarrow T_H2$ switch would not be antigen-specific, and an individual whose immune system is driven to a T_H2 state by a non-HIV signal would be more susceptible to HIV infection and/or progression to AIDS. The essential points of our model are summarized in Table 1.

Our findings may also have implications for AIDS vaccine strategies, as recently proposed by Dr Jonas Salk (pers. commun.). Salk has combined our findings with the recently published study on low-dose versus high-dose infection of susceptible mice to *Leishmania major*. As was shown by Bretscher and colleagues[37], low-dose immunization with *L. major* 'locks' the immune response in a 'T_H1 phase' with activation of DTH and protection of the animals to rechallenge. Therefore, as Salk suggested, low-dose immunization, which preferentially induces cellular immunity, could be advantageous compared to the high-dose/antibody-inducing protocols currently used in AIDS trial vaccines. The issue is not whether antibodies are good or bad in HIV infection, but whether: (1) cellular is more efficient than humoral immunity and (2) whether the immune system is regulated to maximally generate one

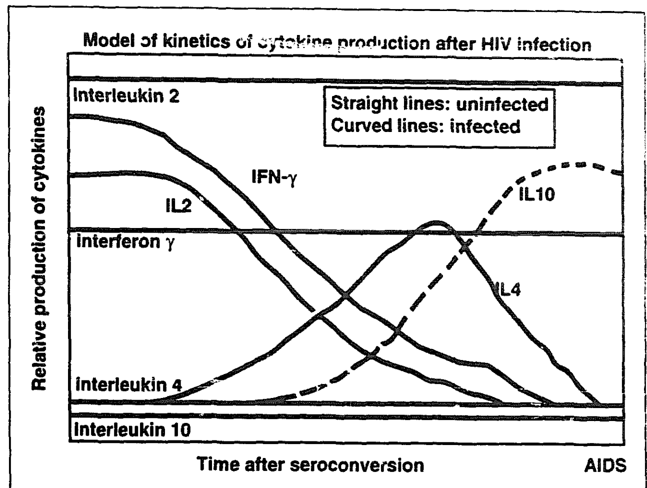

Fig. 2. *Kinetics of cytokine production in stimulated PBMCs from asymptomatic, HIV+ individuals. IL-2 production was in response to influenza virus (a recall antigen that stimulates memory CD4+ T cells). IFN-γ, IL-4 and IL-10 production occurred in response to PHA.*

or the other type but not both types of responses. At present, AIDS vaccine protocols are focused on maximizing both types of T_H responses. However, it remains to be determined whether the 'best of both worlds' can be achieved, and whether 'both world' are more effective than a strong cell and/or humoral-mediated response alone. The early gp160 vaccine trials, in HIV- volunteers started at 40 and 80 μg/individual, did not elicit, or elicited only weak and transient, antibody responses but generated potent HIV specific cellular responses[38]. In subsequent protocols the dose of recombinant gp160 was raised to >640 μg/volunteer[39]. The latter individuals generated both cellular and humoral responses, but no comparisons were made of HIV-specific cellular responses from the two groups of vaccinees. We have compared the *env*-stimulated IL-2 responses generated by the PBMC from the 40 and 80 μg vaccinees with the very best cellular responses generated by asymptomatic HIV+ individuals. The low-dose vaccinees generated a 10-to-100-fold stronger *env*-stimulated IL-2 response than did the selected *env*-reactive, HIV+ individuals[38].

How might the above T_H1–T_H2 model for vaccine development be tested? First, monkeys could be exposed to low doses of simian immunodeficiency virus (SIV), and then rechallenged with lethal doses of SIV. Second, hu-PBL-SCID mice could be adoptively reconstituted with PBL from vaccinees, and then challenged with HIV. Mosier has performed such an experiment and has concluded that the mice transferred with PBL from volunteers with HIV-specific cellular immunity were better protected than the mice reconstituted with PBL from donors with strong HIV-specific antibody responses (pers. commun.). Third, PBMCs from HIV exposed *env*-reactive, seronegative individuals could be compared with PBMCs from unexposed donors for susceptibility to infection with HIV *in vitro*. Fourth, HIV- volunteers could be immunized with low-dose versus high-dose AIDS vaccines and studied for cellular versus humoral immunity. Such volunteers would not be challenged with HIV, but this experiment would permit a vaccine dose-dependent comparison

Table 1. Model of T_H1–T_H2 regulation in resistance and susceptibility to HIV infection and AIDS progression

T_H1–T_H2 state	Cytokines	Description of T_H1–T_H2 relative to HIV and AIDS
$T_H1>T_H2$	IFN-γ; IL-2	Dominance of T_H1-type responses over T_H2-type and protection against intercellular HIV transmission or infection.
$T_H2>T_H1$	IL-4; IL-10	Dominance of T_H2-type response over T_H1-type response and susceptibility to intercellular HIV transmission or infection.
$T_H1>T_H2$ to $T_H2>T_H1$	IFN-γ; IL-2 replaced by IL-4; IL-10	An individual can switch from $T_H1>T_H2$ to $T_H2>T_H1$ by immunological stimuli unrelated to HIV. Such 'cofactors' increase T_H2 cytokines and susceptibility to intercellular transmission or infection by HIV.
HIV-specific T_H1 activation	$IL\text{-}2^{HIV}$	Exposure to or infection with low doses of HIV activates T_H1-type but not T_H2-type response. This T_H1-type response to HIV antigens primes the immune system for T_H1-type protection against subsequent infection with higher doses of HIV.

$IL\text{-}2^{HIV}$: IL-2 production in response to HIV antigens.

of cellular and humoral immunity, including T-cell proliferation, IL-2 production, CTL generation and antibody titer.

Vaccine trials are in progress in an attempt to enhance HIV-specific immunity in individuals who are already infected[39]. The objective in these 'immune-based therapy' protocols is to enhance both cellular and humoral immunity in an attempt to prevent the development of AIDS symptoms. On the basis of the findings summarized here, we suggest that these patients should first be categorized for T_H1- and T_H2-type responses as well as for HIV-specific immunity. We also raise the possibility that those individuals who are 'type –/+/+' could be given anti-IL-4 and/or anti-IL-10 antibody in an attempt to move them into a T_H1 stage, before immunization. Finally, if HIV-specific T_H1 responses are more protective against HIV infection and/or progression to AIDS than antibodies (or even as protective), then the concern surrounding the development of an effective AIDS vaccine may not be justified, because this pessimism is based on the fact that the main neutralizing antibody site is the V_3 loop region of *env*, which is also a hypervariable region. In contrast, cell-mediated immunity involves many HIV epitopes, including those in conserved regions of HIV.

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Proteoglycans on endothelial cells present adhesion-inducing cytokines to leukocytes

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Leukocyte recruitment from the blood circulation into tissue is essential for effective immune responses, and is, consequently, carefully regulated. In this article Yoshiya Tanaka and co-workers describe a model in which proteoglycans on the luminal surface of endothelium capture pro-adhesive cytokines. These cytokines provide the adhesion-inducing signal to particular leukocyte subsets which initiates their transmigration.

There are four central elements in the model we outline here. (1) Leukocyte entry into tissue involves a cascade of molecular events, in which leukocyte adhesion plays a critical role. (2) Cytokines produced within the tissue are important inducers of leukocyte subset-specific adhesion. (3) Pro-adhesive cytokines recruit leukocytes most efficiently when immobilized on the luminal surface of endothelium rather than in solution. (4) Proteoglycans on the luminal surface of endothelium are major participants in this process, responsible for immobilization of pro-adhesive cytokines. We review these elements, emphasizing the issue of cytokine immobilization and particularly our concept of proteoglycan involvement in that process.

Adhesion triggering in leukocyte–endothelial interactions

Cell migration from circulation into tissue, which is essential for immune responses, is understood to involve a co-ordinated sequence of events stabilizing molecules both on the leukocyte and on the endothelium. This so-called 'adhesion cascade', which is generally similar for all leukocytes (for example, granulocytes and lymphocytes) has been well reviewed[1–6]. The first step is loose binding ('tethering') of leukocyte to endothelium via one of the selectin family of molecules. The second step is triggering, in which a signal transduced to the leukocyte converts the functionally inactive integrin molecules to an active adhesive configuration. The third step is strong adhesion mediated by a leukocyte integrins binding to endothelial cell ligands.

Cytokines as adhesion triggers

The first and last steps in the cascade are fairly well defined with respect to leukocyte receptors and endothelial counter-receptors. Much less is known about the physiologically relevant molecules involved in the triggering step. There is great diversity in the molecules on leukocytes which can mediate adhesion[3,5,6]. However, few are proven to be relevant to interactions with endothelium, so far only two cell surface molecules on the endothelium have been demonstrated to trigger integrin adhesion; the lipid mediator platelet activating factor (PAF) and E-selectin (ELAM-1) do so when they bind granulocytes[4,7].

Cytokines are emerging as excellent candidates for physiological 'adhesion triggers'[3,8,9]. They are released at sites of inflammation, act at short distances and induce inflammatory infiltrates of leukocytes *in vivo*[9–12]. Although some cytokines promote adhesion by increasing the surface expression of adhesion receptors and/or ligands, in this review we discuss other cytokines that, by a different mechanism, increase integrin avidity acutely. Rapid cytokine triggering of integrin-mediated adhesion has been demonstrated in neutrophils, monocytes and, recently, T cells[3,10,13–16]. Here, cytokines which trigger adhesion will be referred to as pro-adhesive cytokines. Although pro-adhesive effects are not restricted to a single cytokine family, cytokines of the chemokine (or intercrine) family are proving particularly important. For example, the chemokine interleukin 8 (IL-8) can trigger granulocyte adhesion to endothelial ligands via β2 integrins[8,17] and the chemokine macrophage inflammatory protein (MIP-1β) can trigger adhesion of T-cell subsets to the vascular cell adhesion molecule (VCAM-1) via β1 integrins[16]. The potential importance of chemokines in inflammatory responses is supported by findings that IL-8, MIP-1β and various other chemokines are produced in large amounts by activated lymphocytes,

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