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Type 1 and Type 2 Cytokines in HIV Infection – A Possible Role in Apoptosis and Disease Progression

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The progression of HIV-infected subjects to AIDS was recently postulated to be controlled by the balance between type 1 cytokines (mainly enhancing cell-mediated immunity) and type 2 cytokines (mainly augmenting antibody production). Thus, progression of HIV infection was suggested to be accompanied by a decline of *in vitro* production of interleukin-2 (IL-2), IL-12 and interferon gamma (IFN-γ) (type 1 cytokines) and an increase in the production of IL-4, IL-5, IL-6 and IL-10 (type 2 cytokines) by peripheral blood mononuclear cells of HIV-seropositive patients. According to this hypothesis, clinical markers of progression would be considered the loss of the ability to elicit a delayed-type hypersensitivity reaction to ubiquitous antigens (secondary to defective IL-2 production), hyper-IgE (secondary to increased IL-4 production) and hypereosynophilia (secondary to increased IL-5 production). The type 1 to type 2 shift was suggested to be predictive for the following events: (i) reduction in CD4 counts; (ii) time to AIDS diagnosis; (iii) time to death. Support for this hypothesis stems from the recent observation that a strong type 1/weak type 2 cytokine production profile was observed in HIV-seropositive patients with delayed or absent disease progression, whereas progression of HIV infection was characterized by a weak type 1/strong type 2 cytokine production profile. PBMC of HIV-seropositive individuals are susceptible to antigen-induced cell death (AICD) after antigen recognition via T-cell receptor (TcR). While TcR-induced AICD is seen in $CD4^+$ and $CD8^+$ cells programmed cell death induced by recall antigens is preferentially observed in $CD4^+$ cells, a situation more closely resembling the CD4 depletion of HIV infection. Because type 1 cytokines reduce, whereas type 2 cytokines augment T-lymphocyte AICD, an increase in the concentration of type 2 cytokines could result in the decline in $CD4^+$ cells seen in HIV infection.

Key words: AIDS; apoptosis; cytokines; disease progression; HIV; immunology.

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Introduction

Human immunodeficiency virus (HIV) infection is associated with a profound dysregulation of the immune system (1). Interestingly, functional hyperactivation of humoral immunity (HI) is observed in patients showing signs of defective cell-mediated immunity (CMI) (1). Thus, hypergammaglubulinaemia with hypereosinophilia and hyper-IgE are associated with impaired delayed-type hypersensitivity (DTH) reactions to common recall antigens (2, 3). Because different cytokines are known to stimulate mainly either CMI or HI (type 1 and type 2 cytokines, respectively) (2, 3), cytokine production by peripheral blood mononuclear cells (PBMC) of HIV-seropositive individuals was analysed. The results suggested that type 1 cytokine production is defective and type 2 cytokine production is enhanced in HIV-seropositive individuals, and that the degree of this disequilibrium might be predictive for progression of HIV infection to the acquired immunodeficiency syndrome (AIDS).

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Type 1 and Type 2 Cytokines in the Progression of HIV Infection

T-helper (TH) lymphocytes have been functionally divided into two subsets based on the cytokines they produce; these subsets are named T-helper 1 and T-helper 2 (TH1 and TH2) (4, 5). Because cytokines are produced by cell types other than T lymphocytes a functional definition was introduced; thus, type 1 cytokines mainly stimulate CMI whereas type 2 cytokines mainly stimulate HI. IL-2, IL-12, IFN-γ and probably IL-15 are type 1 cytokines; IL-4, IL-5, IL-6, IL-10 and IL-13 are type 2 cytokines (2, 3). Defective antigen- and mitogen-stimulated IL-2 production has been described in HIV infection since 1985 (6, 7). Analyses of defective IL-2 production have shown that subtle and complex defects in TH function can be detected independently of a decline in CD4 counts, and before the onset of symptoms (7). Thus, when PBMC of asymptomatic HIV-seropositive individuals are stimulated *in vitro* with recall antigens, HLA alloantigens and mitogens, and IL-2 production is measured, different degrees of impairment in TH function are observed. To summarize: (i) IL-2 can be produced in response to all antigens; (ii) recall antigen-stimulated IL-2 production can be selectively defective; (iii) only phytohaemagglutinin (PHA)-stimulated IL-2 production can be observed; and (iv) the ability to produce IL-2 can be completely lost (2, 3). Approximately two-thirds of HIV-seropositive asymptomatic individuals show one or more of these TH functional defects without exhibiting a critical reduction in the number of $CD4^+$ T lymphocytes. These different degrees of impairment in IL-2 production are secondary to the different antigen-presenting cell–TH cell interactions required for the diverse antigens (2, 3), and are predictive for the following: (i) rate of decline in the number of $CD4^+$ T lymphocytes; (ii) time to diagnosis of AIDS; and (iii) time to death (8, 9). Therefore, defects in IL-2 production are predictive for three clinically relevant end-points in HIV infection and progression to AIDS (8, 9).

Because in HIV infection IL-2 production is defective (and IL-2 mainly stimulates CMI) and HI is abnormally activated and because different cytokines stimulate CMI or HI, a number of laboratories examined type 1 and type 2 cytokine production by PBMC of HIV-seropositive individuals. The results observed in some laboratories suggested that, beside IL-2, IL-12 is also severely defective in HIV infection (IFN-γ has been reported by different groups to be either defective or augmented) (2, 3), whereas the production of type 2 cytokines IL-4, IL-5, IL-6 and IL-10 is enhanced (2, 3). Because different cytokines are responsible for diverse biological effects, the concentration of IgE (IL-4 driven) and eosinophils (IL-5 driven) was analysed in HIV-seropositive individuals. As expected, hyper-IgE (2, 3) and hypereosinophilia (2, 3) were detected in those patients in whom defective (IL-2, IL-12 and IFN-γ driven) DTH to common recall antigens is present (2, 3). Additionally, hyper-IgE and hypereosinophilia were recognized as predictors of poor prognosis in HIV-seropositive individuals. These data led to the formulation of the hypothesis that a type 1 to type 2 cytokine shift is present in HIV infection. This hypothesis was met initially by some critiques, the most relevant of which was raised by Dr Fauci's group, who analysed cytokine production in unstimulated PBMC of HIV-seropositive individuals by polymerase chain reaction and could not observe such a shift (10), but has recently been widely accepted. Corollary to the hypothesis is the prediction that strong type 1 cytokine production and well-preserved CMI would correlate with lack of disease progression.

Because HIV infection can result in different clinical outcomes (11), markers of progression and protection were analysed in HIV-seropositive individuals progressing toward AIDS and in the minority of those patients, defined long-term nonprogressors (LTNP), who do not show signs of disease and maintain stable CD4 counts, despite a long-lasting HIV infection. Type 1 and type 2 cytokine production was examined in paediatric and adult cohorts to analyse similarities and differences between vertically transmitted and adult-acquired HIV infection. In both cohorts data obtained in two groups of individuals were compared: (i) asymptomatic HIV-seropositive individuals infected for more than 8 years with a CD4 count more than 500 μL; and (ii) patients with progressive HIV infection as indicated by presence of symptomatology; and/or CD4 counts less than 450 μL. Both in adult-acquired and vertically transmitted infection type 1 cytokine production was observed to be significantly augmented and type 2 cytokine production significantly reduced in HIV-seropositive LTNP individuals compared to HIV-seropositive individuals with progressive HIV infection (12, 13). Therefore, cytokine production profiles by *in vitro* PHA-stimulated PBMC can distinguish between HIV-seropositive patients with different patterns of disease progression, in that a type 1 predominance is evident in LTNP patients whereas a type 2 predominance is characteristic of patients with progressive HIV infection. Finally, because the isolation of syncytium-inducing (SI) HIV variants is associated with disease progression (14), the possible correlation between a type 1 to type 2 shift and isolation of these variants was analysed. Recent results show that isolation of SI variants was indeed associated with the weakest type 1 cytokine production, the strongest type 2 cytokine production and the lowest CD4 counts in both adult and paediatric groups of HIV-seropositive patients (15). Thus, the virological and immunological correlates of disease protection and progression are associated variables that define two different subsets of HIV-seropositive individuals.

Cytokines and Apoptosis in HIV Infection

The proposed shift in type 1 and type 2 cytokine production could be directly responsible for the reduction of CD4 counts which is the hallmark of HIV infec-

tion. Thus, after antigen recognition via their T-cell receptor (TcR), HIV T lymphocytes can either classically become activated and proliferate or can undergo antigen-induced cell death (AICD) *in vitro*. Lymphocytes of HIV-seropositive patients are particularly susceptible to TcR-induced AICD (16), and the extent of this AICD can be differentially modulated *in vitro* by type 1 and type 2 cytokines (17, 18). Thus, type 1 cytokines reduce T-lymphocyte AICD; in contrast, type 2 cytokines have either no effect or enhance *in vitro* T-cell AICD (17). Additionally, AICD can be inhibited by antibodies against IL-4 and IL-10, and enhanced by anti-IL-12 (17). Selective stimulation of $CD4^+$ lymphocytes by recall antigens, including peptides of the envelope of HIV, was recently described to induce AICD exclusively in the CD4 subset, a situation that more closely resembles that observed *in vivo* (17). Even in this scenario, AICD was oppositely modulated by type 1 and type 2 cytokines, or by the neutralization of type 1 or type 2 cytokines (17). AICD was verified to be effected by lymphotoxin; lymphotoxin was also found to be responsible for a soluble-factor-mediated amplifying loop which causes AICD in innocent-bystander lymphocytes (17). Thus, impaired production of type 1 cytokines and augmented generation of type 2 cytokines characteristic of HIV infection could contribute to the destruction of CD4 lymphocytes; this destruction would be mediated by lymphotoxin. Briefly, antigen stimulation of lymphocytes of HIV-seropositive individuals in the presence of abnormally low concentrations of IFN-γ, IL-2 and IL-12, and/or of abnormally elevated concentrations of IL-4 and IL-10, would result in the induction of AICD instead of in the induction of T-cell proliferation. This aberrant process could contribute to the progressive decline of $CD4^+$ T lymphocytes observed in HIV infection. It is important to conclude this part by underlying the facts that: (i) this intriguing hypothesis is based on *in vitro* observations; and (ii) direct HIV-dependent cytopathy has an undeniable role in the killing of HIV-infected CD4 lymphocytes.

Conclusions

The data summarized in this brief review underline the role of the immune response in controlling the progression of HIV infection to AIDS, and the pivotal role of the qualitative and quantitative defects of the immune system in the pathogenesis of this disease. Because of the importance of the immune response in controlling HIV, we believe that antiretroviral therapies will not successfully eradicate HIV and that HIV-seropositive patients will not be ultimately cured unless therapies aimed at restoring the immune system are associated with the antiretroviral drugs currently employed. Thankfully, a number of different immunomodulators are currently being examined in small clinical trials.

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