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EDITORIAL REVIEW

Interference with immune function by HTLV-1

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INTRODUCTION

Viral infections are known to produce a wide spectrum of immune perturbation, ranging from a transient and usually innocuous leucopenia to the devastating immunodeficiency of HIV-1. HTLV-I (Human T-cell lymphotropic virus type 1), which is associated with ATL (Adult T-cell leukaemia/lymphoma) and HAM/TSP (HTLV-I-associated myelopathy/tropical spastic paraparesis), was the first human retrovirus discovered[1], but the effect of HTLV-I infection on the immune system has been less clear. It is well documented that patients with ATL have severe immunosuppression and are prone to other malignancies and opportunistic infections [2–4]. However, evidence has been accumulating that HTLV-1 can cause a clinically important degree of immune suppression even in the absence of malignant disease.

An antiviral immune response usually involves a dominant Th1-type response whereas an optimal immune response to a macroparasite such as a helminth usually involves a dominant Th2-type response. Hence these differing requirements may conflict in a host who is dually infected with both types of pathogen. The overall effect of these conflicting requirements on the course of both infections depends on the natural biology of the pathogens and the immune response to each respective pathogen. For example, the balance of Th1 and Th2 cells is presumably determined by (among other factors) the abundance, distribution within the body and the rate of replication of the respective pathogen. The study by Porto *et al*. in this issue of *Clinical and Experimental Immunology* [5] on the effects of HTLV-I coinfection with schistosomiasis provides an interesting example of such a coinfection.

HTLV-I elicits a strong Th1-type response. Previous work [6] had shown that there appeared to be a high frequency of Th1 cells in the peripheral circulation of HTLV-I-infected subjects, but the HTLV-1-specific response was not studied. More recently, a strong bias to a Th1 phenotype has been shown in the HTLV-1-specific $CD4^+$ cells themselves. Furthermore, the frequency of such cells was significantly larger in HAM/TSP patients than in asymptomatic carriers of HTLV-1 [7–9]. These HTLV-1-specific CD4+ T-cells are able to secrete IFN-γ, TNF-α and IL-2 upon encountering cognate antigen. They possess the phenotype of effector memory cells as defined by Sallusto *et al.* (unpublished observation), i.e. CD45RA-, CCR7-, CD27-, CD28-, which suggests that they would act efficiently as effector cells in the peripheral tissues. The interpretation that a type 1 T-cell response is beneficial in HTLV-I infection is also favoured by recent evidence that the CTL response to HTLV-1 is protective:

- Dominant protection in HTLV-1 infection in Japan is associated with HLA-A2 and -Cw8 [10–12]. That is, individuals who possess either HLA-A*02 or HLA-Cw*08 have a lower proviral load of HTLV-1 and a lower risk of HAM/TSP.
- There is more rapid CTL-mediated lysis of HTLV-1-infected cells in individuals with a low proviral load (Asquith *et al*. unpublished observation).
- Circulating CD8 + cells in individuals with a low HTLV-1 proviral load show consistently higher levels of expression of genes that encode proteins involved in CTL-mediated lysis (Vine *et al*. unpublished observation).

Chronically infected subjects with helminthic parasites such as *S. stercoralis* and *S. mansoni* have been shown to exhibit a Th-2 type response in which there is high production of IgE, IL-4, IL-5, IL-10 and IL-13. Interestingly, although it is thought that a Th2 response is protective in clearing *S. mansoni* infection by the formation of eosinophilic granulomas, the hepatic fibrosis seen in chronic schistosomiasis infection may also be due to this Th2 type response. IL-13 has been shown to be important in the pathogenesis of the fibrosis [13,14].

A strong Th2 response to a helminth influences Th1 responses. For example, Cooke *et al.* [15] have found that *S. mansoni* infection of NOD (nonobese diabetic) mice prevented the onset of Th1-mediated type 1 diabetes. This mechanism appears to involve increased IL-10, decreased IL-12, increased NKT-cells or possibly regulatory T-cells [16]. However, infections that elicit a Th1 response, such as LCMV, can also prevent diabetes in NOD mice [17,18], suggesting that the risk of this autoimmune disease is not simply determined by a balance between Th1 and Th2 responses. A strong bias to a Th1-type response might similarly be expected to impair the Th2-type immune response to parasites such as *S. mansoni* and would therefore presumably increase the parasite burden; however, Th1 bias might also lessen the morbidity due to the Th2-induced fibrosis.

The observations made by Porto *et al*. [5] fulfil some of these predictions, but not all. First, the authors found a greater prevalence of *S. mansoni* infection in HTLV-1-infected subjects than in

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HTLV-1 seronegative controls. However, the cases of *S. mansoni* were ascertained not by serology but by detection of egg excretion in the stool. Therefore these observations imply that HTLV-1 infected individuals are either more susceptible to initial infection with *S. mansoni* or are less able to clear the parasites, and a higher proportion of hosts become chronic excretors of schistosome eggs.

Secondly, as predicted, there was less fibrosis associated with *S. mansoni* infection in individuals coinfected with HTLV-1. Thirdly, Porto *et al*. [5] found a higher rate of treatment failure in individuals coinfected with HTLV-1 and *S. mansoni* than in *S. mansoni* infected subjects alone.

The most unexpected observation was the lower rate of egg excretion in the stool in coinfected individuals. This observation suggested that, contrary to expectation, there was a *lower* parasite burden in the coinfected host. We suggest two possible explanations of this paradoxical finding. First, there is evidence in mice that IL-4 – a type 2 cytokine – is required for efficient translocation of eggs from the mesenteric venules through the intestinal wall and subsequent excretion [14]. A strong type 1 T-cell response elicited by HTLV-1 infection might inhibit IL-4 production and therefore reduce the rate of excretion of schistosome eggs. Second, if HTLV-1 does indeed impair the efficiency of the immune response to *S. mansoni*, then even individuals with a low parasite burden may be unable to control the parasite replication, and so remain chronic excretors of eggs, albeit at a low density in the stool. Therefore, HTLV-1 infected individuals would have a lower mean rate of egg excretion than individuals without HTLV-1 infection.

So far, the most consistent evidence for a degree of immunomodulation by HTLV-I has been seen in coinfection with another helminthic parasite, *Strongyloides stercoralis*. In HTLV-1 coinfection with *S. stercoralis*, there is evidence for an increased rate of chronic carriage, an increased parasite load and more severe disease which is refractory to normally curative treatment [19–24].

HTLV-1 coinfection with TB is also interesting, as there is evidence for a decreased DTH (delayed type hypersensitivity) response to PPD (purified protein derivative) in HTLV-1-infected people [25–27]. Whether this decreased PPD response is associated with an increased risk of reactivation of tuberculosis among HTLV-1-infected patients is not clear but there are reports of increased prevalence of HTLV-1-seropositivity among inpatients with tuberculosis from South America where both infections are endemic [28]. Mortality from tuberculosis was also increased in the HTLV-1 coinfected patients in this study. HTLV-1 coinfection with *M. leprae* has also been studied and there is evidence to suggest an increased prevalence of clinical leprosy among coinfected patients [29–31]. Furthermore, there has also been a report of increased mortality among coinfected patients compared to *M. leprae* infected patients alone [32].

There is also an infective dermatitis seen in Caribbean children infected with HTLV-1, where normally commensal *Streptococcus* species and *Staphylococcus aureus* cause an acute exudative disease [33]. Norwegian (crusted) scabies has also been associated with HTLV-1 infection [34,35].

We have considered above the evidence that HTLV-1 infection alters the immune response in schistosomiasis. The converse may also be true: that is, the immune response to schistosome parasites might impair the immune response to HTLV-1 or other viruses [36]. This possibility could be tested by measuring the proviral load of HTLV-1 in individuals with and without schistosomiasis: a higher mean proviral load would imply a degree of impairment of the immune response. Furthermore, it is possible that the order in which the two infections are acquired might determine the balance of the immune response in a coinfection, and therefore the clinical outcome of the infections.

In conclusion, there is increasing evidence that subjects chronically infected with HTLV-1, even in the absence of malignant disease, have a degree of immunomodulation that has significant effects on infection with several different pathogens. HTLV-1 infection appears to affect the immune system in a multitude of complex pathways which are just beginning to be discovered: these effects differ according to the pathogens encountered by the host.

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