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Suppression of immune responses by dendritic cells infected with HIV

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SUMMARY

Evidence of human immunodeficiency virus (HIV) replication both in the skin Langerhans' cells of AIDS patients (Tschachler *et al.*, 1987) and in normal, peripheral blood dendritic cells (DC) (Patterson & Knight, 1987; Knight & Patterson, 1989) suggests that infection of these antigen-presenting cells may contribute to the immunosuppression seen in AIDS. Support for this hypothesis is now provided by experiments in which the capacity of DC infected *in vitro* to present mitogen to normal syngeneic lymphocytes was measured. Infecting DC with HIV before culturing with lymphocytes inhibited mitogen-stimulated cell proliferation. Viral DNA was detected in DC in these cultures by *in situ* hybridization but, in addition, HIV was also present in a small proportion of lymphocytes. However, introducing an inhibitor of virus replication, 2',3' dideoxyadenosine, after infection of the DC but before culturing with lymphocytes, blocked growth of HIV in lymphocytes. In these latter experiments mitogen proliferation responses were still suppressed. Infection of DC could, therefore, cause immunosuppression in AIDS, both by direct effect on antigen-presentation and by the transfer of HIV to T cells.

INTRODUCTION

Many viruses cause transient immunosuppression, which is believed to be due to infection of lymphocytes (Denman, Bacon & Pelton, 1983). In AIDS, CD4-positive T cells can be latently or lytically infected by HIV and the ensuing depletion of these cells is thought to lead to fatal immunosuppression. However, evidence is now accumulating to suggest that an additional effect of HIV could be to compromise the function of antigen-presenting cells. For example, DC isolated from normal peripheral blood are susceptible to infection with HIV (Patterson & Knight, 1987; Knight & Patterson, 1989). In the peripheral blood of AIDS' patients a reduction in the number of DC expressing high levels of class II MHC antigens and defects in both stimulator as well as responder function in mixed leucocyte cultures were observed (Eales *et al.*, 1988). Patients with AIDS may also have skin Langerhans' cells grossly infected with virus (Tschachler *et al.*, 1987) and these cells show a reduction in the expression of class II histocompatibility antigens (Belsito *et al.*, 1984). Langerhans' cells are precursors of some DC in lymph nodes and can acquire antigens, travel to the lymph node as veiled cells in the afferent lymphatics and present antigen to T cells in the paracortical areas of the lymph nodes (Kelly *et al.*, 1978; Knight *et al.*, 1982; Macatonia, Edwards & Knight, 1986; Macatonia *et al.*, 1987; Silberberg-Sinakin *et al.*, 1976). There may be an absolute requirement for DC to present antigen in primary responses to alloantigens or contact sensitizers (Austyn, 1987; Steinman *et al.*, 1986; Macatonia *et al.*, 1986, 1987). In addition, DC present viral antigens of herpes simplex (Dickson, 1985) or influenza virus (Macatonia *et al.*, 1989) to initiate primary immune responses in mice. They are also potent at stimulating secondary responses to many antigens, including influenza in human or mouse lymphocytes *in vitro* (Austyn, 1987; Knight & Patterson, 1989; Macatonia *et al.*, 1989). *In vitro* studies showed that infection of an antigen-presenting cell line with HIV reduced its capacity to stimulate the proliferation of T cells induced by concanavalin A (Con A) or by anti-CD3 monoclonal antibody (MAb) (Petit *et al.*, 1988). Our studies were designed to test whether infection of normal human DC with HIV impaired their antigen-presenting function.

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MATERIALS AND METHODS

Preparation of cells

Peripheral blood (40 ml) was taken from normal individuals (laboratory workers), defibrinated in plastic bottles and diluted in medium (RPMI-1640 Dutch modification, with 100 IU penicillin and 100 μg/ml streptomycin). DC were obtained by the method reported previously (Knight *et al.*, 1986). Briefly, mononuclear cells were separated on Ficoll. The cells from the interface were incubated overnight in medium with 10% FCS, on petri-dishes (Nunc, Gibco, Uxbridge) at 37° in a CO_2 incubator. The non-adherent cells were removed and layered onto hypertonic metrizamide gradients (14·5 g metrizamide; Nyegaard, Oslo, Norway; plus 100 ml medium) and centrifuged for 10 min at 600 *g*. The interface cells were collected and washed in medium. These preparations were incubated at 37° and DC

were counted and distinguished from monocytes by the veiled morphology of DC in counting chambers. This preparation contained DC at 30–50% purity, and had fewer than 3% lymphocytes, with remaining cells mostly monocytes. In this system the contaminating monocytes have previously been shown to have no effect on the Con A response (Knight & Patterson, 1989).

Human immunodeficiency virus (HIV)

Infectious virus was stored at −70° as culture supernatant from H9 cell lines persistently infected with HIV strains IIIB, RUT or RF (Popovic *et al.*, 1984).

HIV infection of DC

DC ($0{\cdot}5$–1×10^6) were incubated with 10^3–10^6 $TCID_{50}$ units of HIV strain IIIB, RUT or RF, in 200 μl of culture supernatant for 2 days at 37° and washed three times before use. Control DC were incubated in culture supernatant without virus.

Con A-induced lymphocyte proliferation responses in vitro

Cultures in 20 μl hanging drops in Terasaki plates (Knight, 1987) contained 25–100×10^3 human peripheral blood lymphocytes (PBL) and DC (1000) either untreated or treated with HIV, as indicated. Some cultures contained Con A ($0{\cdot}05$–5 μg/ml) and 2′,3′-dideoxyadenosine (ddA, 100 μM) which has anti-viral activity (Mitsuya & Broder, 1986). After 3 days, cultures were pulsed with [^{3}H]thymidine ([^{3}H]TdR) (Amersham International, Amersham, Bucks; 2 Ci/mM, 1 μl added per culture to give a final concentration of 1 μg of TdR/ml) for 2 hr and were harvested by blotting onto filter discs which were counted in a beta-scintillation counter. Differences between treatments above replication variability were assessed by analysis of variance (Knight, 1987).

Alkaline phosphatase anti-alkaline phosphatase (APAAP) labelling combined with in situ *hybridization*

In some experiments, 10 identical hanging drops from Con A proliferation cultures within a group were pooled, washed twice in PBS containing sodium azide ($0{\cdot}01\%$) and cells were labelled for 30 min on ice with a mixture of four monoclonal antibodies recognizing CD19, CD14, CD16, and CD5 determinants which are specific for B cells, monocytes, NK cells and T cells, respectively. After washing the cells they were adsorbed onto $0{\cdot}01\%$ poly-L-lysine-coated, acid-cleaned, glass slides and fixed with 4% paraformaldehyde in $0{\cdot}1$ M phosphate buffer, pH $7{\cdot}2$, for 30 min. Antibody binding was detected by the alkaline phosphatase/anti-alkaline phosphatase (APAAP) staining technique (Mason, 1985). DC were identified by the absence of staining. The presence of HIV nucleic acid in these immunolabelled cell preparations was then detected by *in situ* hybridization using an HIV lamda BH10 probe (Hahn *et al.*, 1984) labelled with [^{35}S] ATP and CTP by nick translation (Rigby *et al.*, 1977). The hybridization mixture and subsequent procedures were as previously described (Patterson, Gross & Webster, 1989), except that the probe was denatured after applying the hybridization mixture to the slides by heating to 95° for 6 min.

RESULTS

Capacity of HIV-infected DC to stimulate Con A-induced lymphocyte proliferation

Uninfected DC (1000) enriched from human peripheral blood caused no proliferation of syngeneic lymphocytes (40,000–80,000) as assessed by the uptake of [^{3}H]TdR after culture for 3 days in 20 μl hanging drops (Knight, 1987) (Fig. 1). Addition of $0{\cdot}05$–5 μg/ml Con A caused a dose-dependent proliferation and addition of normal DC gave marked enhancement of these responses (Fig. 1). These effects were highly significant ($P < 0{\cdot}001$) and reproducible. Removal of contaminating macrophages from the added population with anti-macrophage antibody (CD14) plus complement did not change the enhancement (Knight & Patterson, 1989), showing that the major population involved was the DC. The enriched DC population itself did not proliferate in response to mitogen and the numbers of lymphocytes present in this enriched DC population that was added to culture (< 60) was insignificant in comparison with the

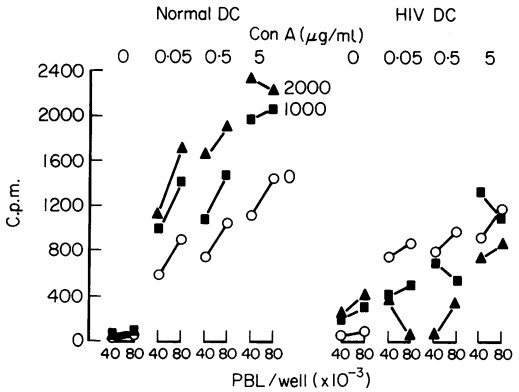

Figure 1. Lymphocyte proliferation with Con A in the presence of HIV-infected DC. (a) The addition of Con A ($0{\cdot}05$–5 μg/ml) to cultures stimulated dose-dependent proliferation of normal human peripheral blood lymphocytes (40–80×10^3/well) (○), after 3 days. Untreated DC (1000, ■; 2000, ▲) markedly enhanced proliferation in the presence of Con A but caused no significant stimulation above background without Con A. (b) DC (1000 ■; 2000 ▲) exposed to HIV inhibit the ongoing Con A proliferation response. These DC in the absence of Con A stimulated low levels of proliferation in normal human PBL.

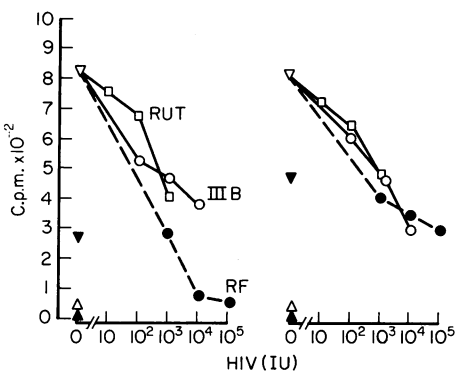

Figure 2. Effect of DC infected with different strains of HIV on lymphocyte proliferation with Con A. 2000 normal DC (▽) enhanced proliferation of syngeneic human PBL (a, 50,000; b, 100,000) in the presence of ($0{\cdot}5$ μg/ml, Con A (▼) but had no significant effect (△) on the background turnover of syngeneic lymphocytes (▲). DC exposed to HIV strains RUT (□), 111B (○) or RF (●) all inhibited Con A-induced lymphocyte proliferation responses. Details as for Fig. 1.

numbers of responder lymphocytes present. When DC were infected for 2 days with 10^4 $TCID_{50}$ units of HIV (strain III B) and washed before addition to lymphocytes in the absence of Con A, there was some proliferation. This suggests that there was a small primary response to viral antigen as seen previously using influenza virus and mouse cells (Macatonia *et al.*, 1989). However, when these infected DC were pulsed with Con A and then cultured with lymphocytes there was inhibition of proliferation, instead of the enhancing effect normally seen with uninfected DC (Fig. 1). This was not due to cell death as most DC remain in culture for 3 or 5 days after infection with HIV, as judged by dye exclusion, and there is little evidence for syncytium formation (Patterson & Knight, 1987). Cells infected with each of three different strains of virus, IIIB, RF and RUT, caused a dose-dependent inhibition of the response (Fig. 2) and 100% block in the enhancement was seen after exposure of the DC to 10^3–10^4 $TCID_{50}$ units of virus.

Effect of HIV infection on the antigen presenting function of DC

Further experiments were undertaken to test whether inhibition of lymphocyte proliferation was due to the virus affecting antigen-presenting function directly or to secondary infection of lymphocytes. In an experiment similar to that described in Fig. 1, lymphocyte proliferation with Con A was enhanced by addition of DC. HIV-infected DC not only prevented this enhancement but also reduced the ongoing response to Con A (Fig. 3). To prevent the infection of lymphocytes by virus from the infected DC, 2′,3′-dideoxyadenosine (ddA) (Mitsuya & Broder, 1986) was added to some cultures after infection of DC but before mixing with lymphocytes. The ddA itself did not interfere with lymphocyte proliferation (Fig. 3). However, infected DC were still unable to enhance Con A responses, suggesting that the virus had a direct effect on the antigen-presentation by DC. A reduction of the ongoing Con A response in the lymphocytes without the added DC was no longer seen (Fig. 3), indicating that part of the original inhibition may be due to infection of activated T lymphocytes.

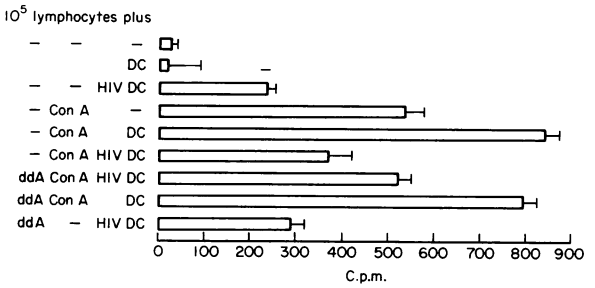

Figure 3. Capacity of HIV-infected DC to enhance lymphocyte proliferation with Con A in the presence of 2′,3′ dideoxyadenosine. 10^5 PBL were cultured for 3 days in 20 μl hanging drops with or without Con A, in the presence of untreated DC (1000) or DC infected with strain 111B (10^4 $TCID_{50}$) *in vitro*. Some cultures contained 100 μM 2′,3′-dideoxyadenosine (ddA) to block infection of lymphocytes (Mitsuya & Broder, 1986).

Identification of cells infected with HIV by *in situ* hybridization

Cells taken from the 20-μl cultures stimulated with Con A for 3 days in the presence of 2% added DC infected with HIV were labelled by the APAAP technique (Mason, 1985) with a cocktail of monoclonal antibodies directed against non-DC (T cells, B cells, monocytes and NK cells). Large cells of DC morphology remained unstained. The same preparations were then examined for HIV infection by *in situ* hybridization. The counts made in one of two experiments giving similar results are shown in Table 1. In cultures without added DC less than 0·1% DC were identified from their morphology and lack of APAAP staining. This increased to between 1% and 2% in cultures with added DC. Many DC were infected with virus and the proportion infected rose to 50% or more in Con A-stimulated cultures. A small proportion of antibody-labelled lymphocytes (< 2%) also contained virus. In cultures containing ddA a similar proportion of DC remained infected but few lymphocytes were positive, showing that infection of lymphocytes had been blocked by the ddA. However, there was still impairment of function (Fig. 3)

Table 1. HIV-infected cells present in cultures detected by *in situ* hybridization

Lymphocytes with	DC $HIV^+/APAAP^-$ APAAP$^-$	DC % infected	Lϕ $HIV^+/APAAP^+$ APAAP+ve	Lϕ % infected	Proportion of DC in population
NDC	0/9		0/823		1·09
Con A	0/1		0/570		0·1
NDC+Con A	0/7		0/720		0·97
NDC+Con A+ddA	0/16		0/901		1·7
HIV DC	3/11	27	13/842	1·5	1·3
HIV DC+Con A	5/10	50	9/560	1·6	1·7
HIV DC+Con A+ddA	11/16	68	0/784	0	2
HIV DC+ddA	5/17	29	3/892	0·3	1·9

DC added at 2% of total Lϕ population.

Cells present in 3-day Con A-stimulated cultures were identified by the APAAP technique. DC remained unstained. Preparations were subsequently hybridized with the BH10 probe to detect viral nucleic acid.

Cell counts from one of two experiments giving similar results are shown in the table. NDC, untreated DC; HIV DC, DC pulsed for 2 days with 10^4 infectious units of HIV (H9-111B) before addition to cultures. Some cultures contained 100 μM/ml ddA.

confirming that reduction in the proliferative response was not due solely to transfer of virus from DC to lymphocytes but resulted from infection of DC directly or via materials released into the culture from infected DC.

DISCUSSION

Our results indicate that there may be a direct effect of HIV infection of DC on the antigen-presenting function of these cells. Previous studies have shown that when these enriched DC were exposed to the IIIB stain of HIV *in vitro* in short-term cultures (up to 6 days) the DC but not the macrophages were productively infected, as shown by electron microscopy (Patterson & Knight, 1987). The relative resistance of macrophages to infection with the IIIB strain of HIV is also inferred from the observation that macrophages are 10,000-fold less susceptible to productive infection than lymphocytes (Nicholson *et al.*, 1986). In the present experiments infection of a high proportion of DC was confirmed by *in situ* hybridization using radiolabelled DNA probes (Table 1). Taken together with the observation that DC and not macrophages enhance Con A responses, the major immunosuppressive effect is almost certainly operating through the DC in the enriched population of antigen-presenting cells. The inhibition of the functional response could be by virus produced in DC blocking CD4 receptors on T cells. However, this seems unlikely as no suppression was seen with heat-inactivated virus (not shown), suggesting that live infectious virus was required.

A reduction in the capacity of low-density peripheral blood cells from AIDS patients to stimulate allogeneic lymphocytes has been described in addition to a reduction in lymphocyte responses (Eales *et al.*, 1988). This suggests that inhibitory effects of HIV via DC can also occur *in vivo*. However, it was not clear whether the reduction of class II levels on the low-density cells from these patients and the low stimulatory capacity was due to a reduction of the class II levels on DC or to a loss in the numbers of DC present. In some AIDS patients a reduction in the numbers of DC isolated from peripheral blood has been observed (S. E. Macatonia, A. J. Pinching, R. Lau and S. C. Knight, unpublished data). Levels of class II molecules on DC varied following HIV infection *in vitro* (Patterson & Knight, 1987) but a reproducible reduction in levels was not observed (S. Patterson, P. A. Bedford and S. C. Knight, unpublished data). In some studies of cells from HIV-infected but asymptomatic individuals, the lymphocytes responded to stimulation with normal allogeneic DC, but the DC from infected individuals caused little allogeneic stimulation (S. E. Macatonia, A. J. Pinching, R. Lau and S. C. Knight, manuscript in preparation), but it is not yet known whether these DC show reduced levels of class II molecules. However, it seems probable that reduction in responsiveness operating via DC may precede the appearance of any T-cell defects.

We also provide evidence that infected DC disseminate virus to the T-helper cell population and can cause some immunosuppression via this secondary infection. Antigen-presenting DC activate T cells by direct contact and act as central cells around which responding T cells cluster (Inaba, Witmer & Steinman, 1984; Knight *et al.*, 1982). This activation process itself may increase the amount of virus present in DC by enhancing the levels of CD4 on DC and so making them more susceptible to infection or by activating latent virus in DC (S. Patterson, unpublished data). Such effects might explain the tendency to see a higher percentage of infected DC in Con A-stimulated cultures (Fig. 1). It is likely that virus replicating in the DC could infect T cells via their CD4 receptors during the close clustering between the cells. Replication of virus in the T cells and further infection of CD4-positive DC (Knight & Patterson, 1989) could then proceed as the T cells are activated via antigen on the DC. The inhibition in the response contrasts with the additive effects usually seen when two stimuli are added to lymphocytes, e.g. increased proliferation was seen when DC pulsed with influenza virus and Con A were added to cultures (Knight & Macatonia, 1988). Our results thus support the idea that in AIDS patients infection of Langerhans' cells or DC, which are vital in presenting antigens for primary responses and potent at presentation in secondary stimulation, could suppress immune response both by a direct effect on their antigen-presenting capacity and by infecting activated T cells. An additional defect in B-cell memory responses caused by the infection of the follicular dendritic cells of the B-dependent areas (Armstrong & Horne, 1984) might then combine to produce the lethal immunosuppressive condition in AIDS patients.

The proliferation induced in lymphocytes by DC infected with HIV could result from non-specific cellular activation by HIV, but is more likely to be a small primary proliferative response since further studies have shown that DC taken from normal peripheral blood and infected with AIDS virus *in vitro* can initiate both proliferative and cytotoxic responses to HIV in syngeneic lymphocytes (manuscript in preparation). Here we show that the capacity of the infected DC to present other antigens is blocked. Aberrant expression of viral antigens on DC due to gross infection of the cells may block the capacity of DC to acquire and present other antigens by a form of antigen competition.

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