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Simian Immunodeficiency Virus Induces Expression of Class II Major Histocompatibility Complex Structures on Infected Target Cells In Vitro

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The human immunodeficiency virus (HIV) and the closely related simian immunodeficiency virus (SIV) induce profound immune dysfunction in primate species. The present studies show that cell populations infected in vitro with SIV exhibit increases in major histocompatibility complex (MHC) class II antigen expression. Cell lines chronically infected with both the monkey and human viruses express substantially more MHC class II but not more lineage-restricted or activation antigens on their membranes than do uninfected cell lines. Furthermore, 2′-deoxy-5-iodouridine increased MHC class II antigen expression on SIV-infected cell lines in parallel with increased expression of viral antigens. MHC class II induction does not appear to be mediated through the production of a soluble factor, such as gamma interferon, by SIV-infected cells. Interestingly, studies of the kinetics of antigen expression by cell lines after SIV infection indicate that the induction of MHC class II structures is a late event. Immunoelectron microscopy revealed that MHC class II antigen is expressed not only on the surfaces of the SIV-infected cells but also on the envelope of virus particles derived from those cells. MHC antigen expression on virus-infected cells and the expression of those determinants by the virus may play a role in the pathogenesis of acquired immunodeficiency syndrome and the autoimmune abnormalities observed in HIV-infected individuals.

The human immunodeficiency virus (HIV) is the etiologic agent in acquired immunodeficiency syndrome (AIDS), and the closely related simian immunodeficiency virus (SIV), previously called simian T-lymphotropic virus type III, induces an AIDS-like syndrome in macaque monkeys (1, 4, 16). The precise mechanisms by which these viruses induce immune abnormalities remain unclear. They infect T4+ (helper/inducer) lymphocytes (11, 12) and cells of the monocyte/macrophage lineage (9). After infection with these agents, a dramatic decrease in the number of circulating T4+ lymphocytes occurs (15, 16). Other consequences of infections with this family of viruses which may account for immune dysfunction remain to be delineated.

Major histocompatibility complex (MHC)-encoded structures on the surfaces of immune cells play a crucial role in the interactions of these cells. MHC class I (MHC-I) cell surface molecules are recognized by T8+ (suppressor/cytotoxic) lymphocytes, and MHC class II (MHC-II) molecules are recognized by T4+ lymphocytes (17). These structures are critically important in the recognition of self by the immune cell. In the present studies we have demonstrated that cell populations infected with SIV exhibit an increase in MHC-II-encoded membrane antigen expression.

MATERIALS AND METHODS

Cells and viruses. The cell lines used were H9, H9 infected with SIV (H9-SIV), HUT78, HUT78 infected with SIV (HUT78-SIV), and H9 infected with two different isolates of HIV (H9-HIV_A and H9-HIV_B). The chronically infected cell lines had been maintained for at least 18 months after infection. The SIV isolate used for acute infection in this study had been isolated from a rhesus monkey with a lymphoma (16). Culture supernatants of phytohemagglutinin-stimulated human peripheral blood lymphocytes infected with this isolate or those of H9 cells chronically infected with this isolate were used as a virus source.

MAbs. Monoclonal antibodies (MAbs) reactive with T1 (24T6G12), T3 (2Ad2A2), T4 (19Thy5D7), MHC-I (W6/32), MHC-II (I-2,949), the interleukin-2 (IL-2) receptor (1HT4), and the T-cell activation antigen Ta.1 (4EL) were kindly provided by S. Schlossman (Dana-Farber Cancer Institute, Boston, Mass.). The anti-T3 MAb SP34 was provided by C. Terhorst (Dana-Farber Cancer Institute). The anti-MHC-II MAb LB3.1 was provided by J. Strominger (Dana-Farber Cancer Institute). All the anti-MHC-II MAbs used recognized HLA-DR.

Cellular radioimmunoassay. Between 2×10^5 and 5×10^5 infected cells and equivalent numbers of uninfected cells were plated per well in triplicate into flat-bottom wells of a flexible 96-well microtiter plate (Becton Dickinson Labware, Oxnard, Calif.) coated with 100 μg of poly-L-lysine (Sigma Chemical Co., St. Louis, Mo.) per ml and incubated for 2 h at room temperature. The cells were dried, 2% bovine serum albumin in phosphate-buffered saline was incubated in each well for 1 h and then 50 μl of MAb was added to the wells for 45 min. The wells were washed two times with phosphate-buffered saline and then incubated for 45 min with 50 μl of ^{125}I-labeled goat anti-mouse immunoglobulin (DAKO, Santa Barbara, Calif.). After four washes with phosphate-buffered saline, the wells were dried and cut, and the radioactivity bound to each well was measured. To detect SIV antigen, a one-step radioimmunoassay was done on these cells by using ^{125}I-labeled immunoglobulin purified from the plasma of a rhesus monkey which had been inoculated with SIV.

Immunoprecipitation and gel electrophoresis. H9 and H9-SIV were surface labeled with 1 mCi of ^{125}I (Amersham Corp., Arlington Heights, Ill.) by the lactoperoxidase method. The labeled cells were solubilized with lysate buffer (1% Triton X-100, 0.05 M Tris hydrochloride buffer (pH 7.2), 0.15 M NaCl, 1 mM EDTA, 1% aprotinin, 1 mM

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TABLE 1. Antigen expression of human T-cell lines chronically infected with SIV or HIV[a]

Antigen[b]	Binding (cpm/cpm [ratio])			
	H9-SIV/H9	HUT78-SIV/HUT78	H9-HIV$_A$/H9	H9-HIV$_B$/H9
T1 (24T6G12)	1,479 ± 233/1,353 ± 75 (1.09)	416 ± 15/531 ± 66 (0.78)	2,923 ± 143/3,028 ± 312 (0.96)	2,275 ± 72/2,730 ± 58 (0.83)
T3 (2Ad2A2)	570 ± 59/455 ± 15 (1.25)	769 ± 44/855 ± 88 (0.90)	2,111 ± 96/1,753 ± 126 (1.20)	1,155 ± 127/970 ± 56 (1.19)
T4 (19Thy5D7)	128 ± 10/724 ± 30 (0.18)	186 ± 9/295 ± 17 (0.63)	238 ± 11/1,221 ± 80 (0.19)	198 ± 38/1,511 ± 95 (0.13)
MHC-I (W6/32)	2,516 ± 20/1,681 ± 151 (1.50)	5,942 ± 402/4,899 ± 94 (1.21)	3,395 ± 347/2,782 ± 272 (1.22)	4,219 ± 331/2,618 ± 513 (1.61)
MHC-II (I-2)	542 ± 50/164 ± 18 (3.30)	2,947 ± 169/782 ± 208 (3.77)	565 ± 69/302 ± 20 (1.87)	462 ± 25/268 ± 23 (1.72)
MHC-II (LB3.1)	1,461 ± 21/433 ± 24 (3.37)	4,609 ± 286/1,931 ± 95 (2.39)	1,972 ± 88/758 ± 86 (2.60)	1,885 ± 264/573 ± 53 (3.29)
MHC-II (949)	2,209 ± 99/436 ± 144 (5.07)	4,436 ± 65/1,783 ± 80 (2.49)	1,110 ± 68/552 ± 84 (2.01)	1,946 ± 101/552 ± 84 (3.53)
IL-2 receptor (1HT4)	418 ± 52/382 ± 47 (1.09)	772 ± 90/679 ± 121 (1.14)	769 ± 41/680 ± 54 (1.13)	860 ± 117/475 ± 52 (1.81)
Ta.1 (4EL)	557 ± 27/567 ± 63 (0.98)	186 ± 19/261 ± 4 (0.71)	885 ± 115/1,354 ± 69 (0.65)	885 ± 103/1,056 ± 176 (0.84)
Control ascites	55 ± 9/52 ± 7 (1.06)	101 ± 12/96 ± 6 (1.05)	74 ± 10/70 ± 9 (1.06)	102 ± 17/76 ± 11 (1.34)
SIV[c]	518 ± 41/61 ± 9 (8.49)	553 ± 38/60 ± 2 (9.22)	101 ± 4/83 ± 13 (1.22)	74 ± 6/66 ± 3 (1.12)

[a] A cellular radioimmunoassay was performed on the cells chronically infected with SIV or HIV and equivalent numbers of uninfected cells.
[b] The particular MAbs used in these studies are noted in parentheses after the antigens.
[c] To detect SIV antigens, immunoglobulin purified from the plasma of a rhesus monkey which was inoculated with SIV was directly labeled with ^{125}I-Na and bound to the cells in the wells.

phenylmethylsulfonyl fluoride), cleared by microcentrifugation, and precleared with rabbit anti-mouse immunoglobulin (DAKO)-coated protein A-Sepharose CL-4B beads (Sigma). Precleared cell lysates were incubated with MAb-coated protein A beads overnight at 4°C. After being washed, immunoprecipitates were eluted from the beads with Laemmli sample buffer and analyzed in a 10% sodium dodecyl sulfate-polyacrylamide gel with a 3.5% stacking gel under reducing conditions. The gels were dried and visualized by autoradiography.

IFN-γ assays. Two different assay systems were used to detect gamma interferon (IFN-γ) in culture supernatants. The induction of MHC-II expression on peripheral blood mononuclear cells from a patient with chronic myelogenous leukemia (CML) was determined after incubation with culture supernatants as a functional assay for IFN-γ (6). A total of 10^6 CML cells were incubated in 1 ml of RPMI 1640 plus 10% fetal calf serum (FCS) containing various concentrations of recombinant IFN-γ (Biogen, Cambridge, Mass.) or culture supernatants of H9-SIV cells at 37°C for 24 h. Each cell sample was then stained with anti-MHC-II MAb (949) or control mouse ascites followed by fluorescein-labeled goat anti-mouse immunoglobulin (DAKO). The mean channel fluorescence of these CML cells was measured by a fluorescence-activated cell sorter (Epics-C; Coulter Electronics, Inc., Hialeah, Fla.). A solid-phase radioimmunoassay for IFN-γ was also done with a commercially available kit (Centocor, Pa.). Briefly, culture supernatant samples were incubated with polystyrene beads coated with a MAb specific for human IFN-γ. These beads were then incubated with an ^{125}I-labeled MAb against human IFN-γ, and the radioactivity bound to the beads was measured.

Kinetic studies of antigen expression. A total of 10^7 H9 cells were incubated at 37°C with supernatants containing SIV or control medium overnight and washed. The infected and uninfected cells were then maintained for 40 to 70 days in RPMI 1640 plus 10% FCS under the same conditions. The cell concentrations of the paired flasks were adjusted to 5×10^5/ml every 3 to 4 days, and antigen expression on these cells was determined at the same time by a cellular radioimmunoassay with MAbs which recognize T1, T3, T4, MHC-I, MHC-II, the IL-2 receptor, Ta.1, and with an SIV-specific heterologous antiserum. A binding ratio was calculated as the radioactivity bound to infected cells divided by that bound to the equivalent number of uninfected cells. Reverse transcriptase activity was measured as previously described (11).

Immunoelectron microscopy. Chronic H9-SIV cells were incubated with an anti-MHC-II MAb (LB3.1) for 45 min, washed, and then incubated with gold-conjugated goat anti-mouse immunoglobulin G (IgG) (Boehringer Mannheim Biochemicals, Indianapolis, Ind.) for 45 min. Cells were washed, fixed with 1% glutaraldehyde in 0.1 M cacodylate buffer overnight, and then processed for electron microscopy. H9-SIV cells incubated with negative-control mouse ascites and gold-conjugated anti-mouse IgG showed no staining with gold particles.

RESULTS

MHC antigen expression on human T-cell lines chronically infected with HIV and SIV. Preliminary studies were performed to determine if human T-cell lines chronically infected with HIV or SIV have alterations in their expression of MHC antigens. Antigen expression on cells was assessed by a cellular radioimmunoassay by using a panel of MAbs (Table 1). The expression of MHC-II antigens recognized by three different MHC-II-specific MAbs was 3 to 5 times greater on the chronically SIV-infected cells than on the uninfected H9 cells. This increase of MHC-II antigen expression was also observed on HUT78-SIV and H9-HIV$_A$ and H9-HIV$_B$. MHC-I antigen expression by H9-SIV and one of the two studied H9-HIV lines was approximately 50% greater than that of uninfected H9 cells; the increase of MHC-I was approximately 20% on HUT78-SIV and the other H9-HIV line when compared with the uninfected cell lines. T4 expression was substantially less on the infected cell lines than on the uninfected cell lines. The expression of other T-cell antigens, including T1, T3, the IL-2 receptor, and the activation antigen Ta.1, varied by less than 35% in the infected and uninfected cell lines. One of the H9-HIV lines showed an 81% increase in the expression of the IL-2 receptor.

Student's t tests were performed on $\log_{10}$-transformed counts-per-minute data to compare the binding of each

antibody to infected and uninfected cells. The four separate experiments shown in Table 1 were combined to facilitate this statistical analysis. T4 expression was significantly lower ($P < 0.005$) and MHC-II, as detected by any of the three MAbs, was significantly higher ($P < 0.05$) on the infected than on the uninfected cells. No significant difference could be demonstrated between infected and uninfected cells in the expression of the other antigens studied. These data suggest that cellular MHC antigen expression, especially class II antigen expression, is specifically increased when the cell is chronically infected with HIV or SIV.

The monkey immunoglobulin used for the detection of SIV antigens did not react in the cellular radioimmunoassay with H9-HIV cells, a population which was strongly positive for MHC antigens. Furthermore, none of the anti-MHC-I or -II MAbs tested blocked the binding of the SIV-specific antibody to H9-SIV cells, nor did the SIV-specific antibody block anti-MHC-MAbs binding to those cells. These data suggest that the apparent increase of MHC expression in the human T-cell lines infected with SIV or HIV was unlikely to represent a serologic cross-reaction between MHC and viral antigens.

Surface-labeled cellular protein from uninfected and H9-SIV cells was analyzed by immunoprecipitation with MAbs followed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (Fig. 1). This study confirmed that MHC-II (29- and 34-kilodalton) and MHC-I (44-kilodalton) molecules were significantly increased on H9-SIV cells compared with uninfected H9 cells, whereas the expression of T3 remained unchanged. The radioactivity (infected/uninfected) of each band, measured by 5-min counts on a gamma counter, was

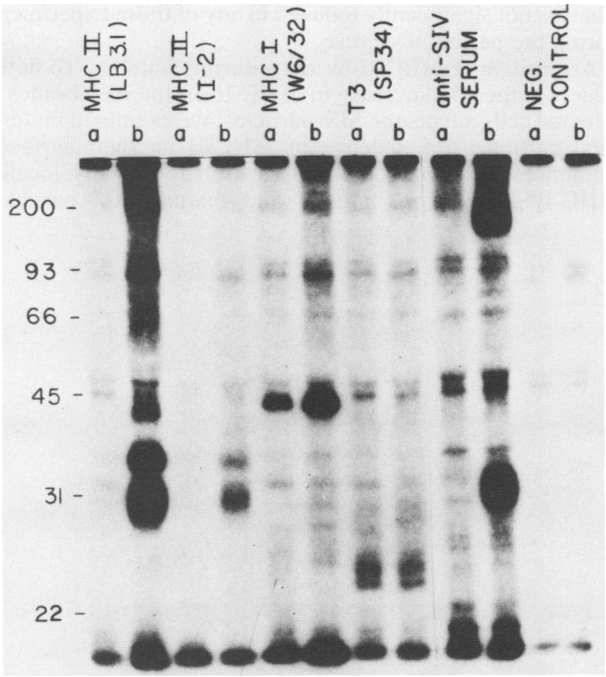

FIG. 1. Cell lysates of ^{125}I-surface-labeled H9 (a) and H9-SIV (b) were incubated with antibody-coated protein A-Sepharose beads, and resulting immunoprecipitates were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Anti-SIV serum was obtained from a rhesus monkey inoculated with SIV. Negative mouse ascites was used as the negative control. Numbers to the left of the gel indicate the molecular mass in kilodaltons.

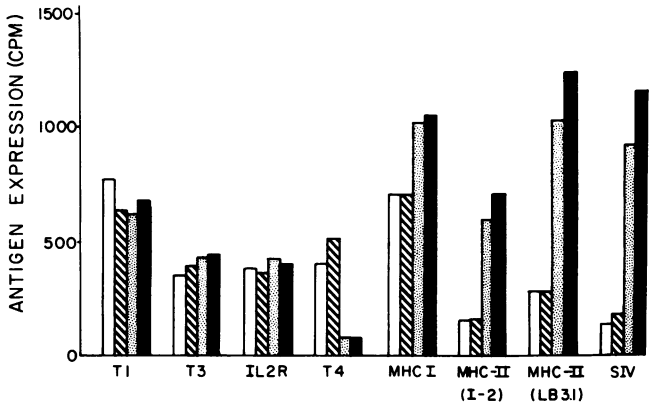

FIG. 2. Induction of antigens on H9-SIV cells with IUDR. H9 and H9 chronically infected with SIV (H9-SIV) were incubated in RPMI 1640 containing 10% FCS with or without 50 μg of IUDR per ml. After 72 h of incubation at 37°C, H9 (□), H9 treated with IUDR (▨), H9-SIV (▤), and H9-SIV treated with IUDR (■) were harvested, and the antigens expressed on equivalent numbers of cells were quantitated by a cellular radioimmunoassay.

as follows: 3,614/540 for MHC-II (LB3.1); 873/428 for MHC-II (I-2); 1,156/568 for MHC-I (W6/32); 476/538 for T3 (SP34); and 1,866/595, and 1,566/427 for anti-SIV serum, with background counts of 200. SIV immune monkey serum precipitated both the 160-kilodalton envelope glycoprotein and the 32-kilodalton transmembrane portion of the viral envelope structure in the control lane.

Induction of MHC and viral antigen expression. 2′-Deoxy-5-iodouridine (IUDR) induces the expression of viral antigens on virus-infected cells. We, therefore, assessed the relationship between MHC and viral antigen expression on H9-SIV cells by inducing viral antigens on chronically infected cells with IUDR. MHC-II and SIV antigens were induced 21 to 26% on H9-SIV cells after a 72-h incubation with IUDR ($P < 0.05$) compared with cells treated similarly, but without IUDR (Fig. 2). No significant increase was observed in the expression of T1, T4, MHC-I, and IL-2 receptors on these cells. Uninfected H9 cells did not show any induction of MHC-antigen expression after treatment with IUDR. These data suggest that increased MHC-II expression is associated with increased SIV antigen expression.

Assessment of IFN-γ in cultures. MHC antigens are induced in some systems through the elaboration of humoral factors, such as IFN-γ, by virus-infected cells (7). The production of such humoral factors inducing MHC-II in the

TABLE 2. MHC-II induction on CML cells with culture supernatants of H9-SIV

Samples[a]	Mean channel fluorescence[b]
Control medium	79.91
IFN-γ (3 U/ml)	95.70
IFN-γ (10 U/ml)	100.47
IFN-γ (100 U/ml)	101.24
Culture supernatant of H9-SIV (25%)	70.47
Culture supernatant of H9-SIV (50%)	64.43
Culture supernatant of H9 (50%)	74.21

[a] Samples were diluted in the control medium (RPMI 1640 plus 10% FCS).
[b] Mean channel fluorescence represents experimental (cells staining positively with an anti-MHC-II MAb) minus control (cells staining positively with a control mouse ascites).

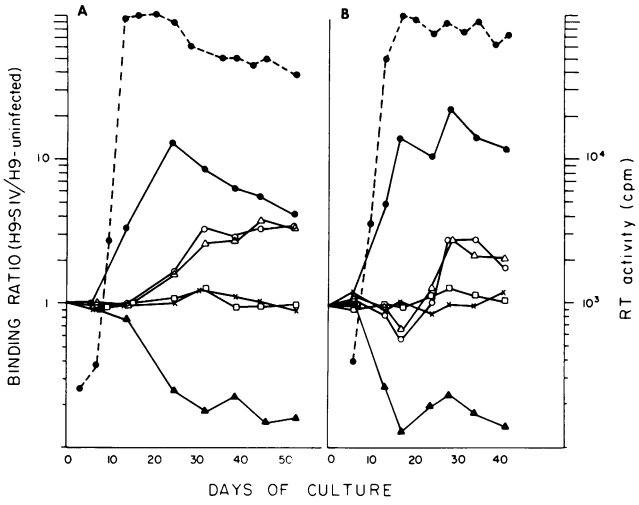

FIG. 3. Kinetics of antigen expression on H9 cells acutely infected with SIV. The antigens shown are MHC-II (I-2) (○), MHC-II (LB3.1) (△), MHC-I (□), T4 (▲), IL-2 receptor (×), and SIV-encoded determinants (●). A binding ratio was calculated as the radioactivity bound to H9-SIV divided by the radioactivity bound to the equivalent number of H9 uninfected cells, as determined by a cellular radioimmunoassay. Reverse transcriptase activity in the infected culture (●- -●) was also monitored. SIV isolates used for infection in this study were culture supernatants of human peripheral blood lymphocytes infected with SIV (A) and culture supernatants of H9 chronically infected with SIV and maintained in RPMI 1640 with 10% FCS (B).

supernatants of H9-SIV was therefore assessed. This was done by using as a functional assay the induction of MHC-II expression on CML cells after incubating culture supernatants of H9-SIV cells (Table 2). The mean channel fluorescence of CML cells stained with anti-MHC-II MAb significantly increased when the cells were incubated with ≥3 U of recombinant IFN-γ per ml. This induction of MHC-II on CML cells was blocked by an anti-IFN-γ MAb (data not shown). MHC-II expression by CML cells incubated with culture supernatants from H9-SIV was not greater than that of CML cells incubated with RPMI 1640 plus 10% FCS. The induction of MHC-II on uninfected H9 cells after incubation with IFN-γ was also assessed. MHC-II induction on H9 cells with IFN-γ was not seen after a 24-h period of incubation. After 72 h of incubation with 300 U of IFN-γ per ml, the percentage of MHC-II-positive cells increased from 5.6 to 13.9%. The culture supernatants of H9-SIV cells, however, did not affect MHC-II expression on H9 cells after 24 or 72 h of incubation. A radioimmunoassay was also done to detect IFN-γ in the culture supernatant of H9-SIV by using a MAb specific for human IFN-γ. No IFN-γ was measurable in H9-SIV culture supernatants by this approach, an assay system sensitive enough to detect 0.5 U of IFN-γ per ml. These data suggest that MHC-II induction on H9-SIV cells is not likely to result from autoregulation mediated by IFN-γ.

Kinetics of MHC-II induction in vitro. We then assessed the kinetics of the expression of MHC-II and viral antigens on H9 cells acutely infected with SIV. H9 cells were incubated with SIV overnight, washed, and then cultured for 40 to 70 days (Fig. 3). Reverse transcriptase activity in the supernatants was detectable by day 10 after infection and reached a peak between days 10 and 20. The kinetics of SIV antigen expression correlated with that of the generation of reverse transcriptase. T4 antigen expression decreased as viral antigen expression increased and thereafter remained low. An increase in MHC-II antigen expression was not observed until between days 20 and 30 after infection. Similar results were seen when the virus source was from an IL-2-dependent human peripheral blood lymphocyte culture or H9 cells chronically infected with SIV maintained in RPMI 1640 plus 10% FCS. In two additional experiments, MHC-II antigen induction first occurred on days 46 and 53, whereas SIV antigen was detected on days 14 and 17, respectively, after infection (data not shown). MHC-I antigen was not significantly induced in any of these experiments during the period of culture.

Acquisition of MHC-II by virus during budding. To determine whether the increase in MHC-II on the membranes of infected cells affects the SIV particles, we examined budding viral particles for evidence of MHC-II on their surfaces. Immunoelectron microscopy was used to visually localize MHC-II antigen on budding and mature SIV particles.

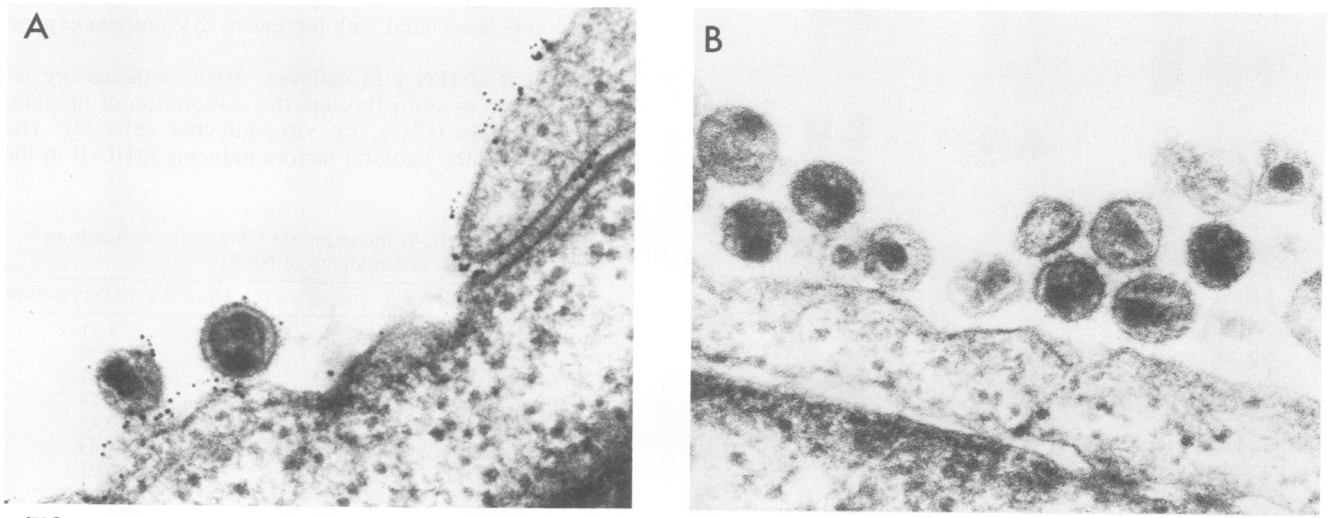

FIG. 4. Electron micrographs of H9-SIV cells incubated with (A) mouse anti-MHC-II MAb or (B) negative-control mouse ascites fluid and then incubated with a gold-conjugated goat anti-mouse IgG serum. Gold particles indicating the presence of MHC-II antigen are aligned along the cell membrane and around the envelope of mature viral particles in panel A but not in panel B.

Virus-infected H9 cells were incubated first with a mouse anti-MHC-II MAb and then with a gold-conjugated goat anti-mouse IgG serum. Gold particles were seen on the surfaces of a significant percentage of infected cells and also on the surfaces of some budding and mature virus particles (Fig. 4). Thus, by this technique it appears that MHC-II antigens may be acquired by some viral particles while budding from cell membranes.

DISCUSSION

The present studies indicate that MHC antigen expression, most strikingly class II antigen expression, is specifically increased when cells are infected in vitro with SIV. SIV and the human AIDS virus HIV are morphologically indistinguishable and antigenically related; SIV and HIV share a tropism for T4+ lymphocytes and both induce analogous immunodeficiency syndromes (3, 10, 11, 16). Therefore, it is likely that the present observations with SIV will also hold true for HIV. In fact, we have shown that MHC-II is increased in H9 cells chronically infected with HIV (Table 1).

Although MHC-I as well as MHC-II antigens are expressed in greater quantity on the surfaces of chronically SIV-infected cells than on uninfected cells, we were unable to demonstrate the induction of MHC-I expression with IUDR or its increased expression after the acute infection of cell lines in vitro. It is therefore not clear whether the infection of cell populations with SIV reproducibly induces MHC-I expression or if such an infection induces MHC-I expression by a different mechanism.

In the present study, we have shown that H9-SIV cells did not produce detectable IFN-γ by using a functional assay system sensitive enough to detect 3 U of IFN-γ per ml and a radioimmunoassay sensitive enough to detect 0.5 U of IFN-γ per ml. MHC-II expression was shown to increase only slightly on uninfected H9 cells when the cells were incubated with high concentrations of exogenous IFN-γ. Furthermore, the increase of MHC-II on H9 cells after infection with SIV occurred long after virus production could be detected by these cells. It is therefore unlikely that the MHC-II induction on H9-SIV cells is mediated by IFN-γ.

The mechanism by which this MHC-II induction occurs remains undefined. It is, however, interesting to speculate that a gene product of SIV might be responsible for regulating this induction. A human T-lymphotropic virus type II-encoded *trans*-activating protein has been recently shown to induce cellular IL-2 receptor expression (5), and HIV has been clearly shown to encode for proteins which similarly can activate gene expression in *trans* (18).

The observation that MHC-II can be acquired by SIV during budding is provocative. This acquisition, while it may be merely passive, might also occur as a result of preferential interaction between viral structural proteins and MHC-II. Furthermore, because MHC-II preferentially recognizes T4, the expression of MHC-II on the surface of the virus might increase the tropism of the virus for T4+ cells. Further studies will be needed to determine whether MHC-II is preferentially acquired by budding virus or is merely passively acquired.

Changes in MHC-II expression by antigen-presenting cell (APC) populations in patients with AIDS has been reported. In fact, MHC-II expression on the circulating monocytes of these individuals has been shown to be substantially less than that of healthy controls (8), and MHC-II expression on Langerhan's cells, the APCs of the skin, is also less in individuals with AIDS than in healthy controls (2). Interestingly, however, and consistent with the findings in the present studies, Heagy et al. (8) showed that MHC-II expression on the monocytes of patients with AIDS-related complex is actually greater than that of normal individuals. Thus, an increased MHC-II expression by APCs may occur in vivo in the early stages of an HIV infection.

It has been suggested that autoimmune mechanisms may play an important part in the pathogenesis of the basic immune defects in AIDS (13). Such potentially autoimmune phenomena as thrombocytopenia, hypergammaglobulinemia, glomerulonephritis, circulating immune complexes, and the generation of circulating anti-lymphocyte antibodies clearly contribute to the morbidity associated with this disease (14). Increased MHC-II expression on virus-infected APC populations might initiate a cycle of increased immune reactivity to self antigens which could lead to these sequelae.

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