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*J Immunol* 2001; 166:1125-1131; doi: 10.4049/jimmunol.166.2.1125

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Transcriptional Down-Regulation of CXC Chemokine Receptor 4 Induced by Impaired Association of Transcription Regulator YY1 with c-Myc in Human Herpesvirus 6-Infected Cells

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We have recently reported that down-regulation of CXC chemokine receptor (CXCR) 4 in CD4+ T lymphocytes is induced by human herpesvirus (HHV) 6 infection. In this study, we further studied the mechanisms of HIV-6-induced CXCR4 down-regulation, focusing on the regulation of CXCR4 transcription. Down-regulation of CXCR4 transcription was detected in HHV-6A-infected JHAN and HHV-6B-infected MT-4 cell lines, as we had previously reported for HHV-6-infected peripheral blood CD4+ T lymphocytes. Luciferase assays revealed that a YY1-binding site around −320 relative to the transcription start site is important for down-regulation of CXCR4 transcription in HHV-6-infected cells. The binding activity of YY1, which is a repressor of CXCR4 transcription, to the CXCR4 promoter appeared to significantly increase in HHV-6-infected cells compared with the binding activity in mock-infected cells. Immunoprecipitation assays showed that in HHV-6-infected cells association of c-Myc with YY1 was decreased and that of Max with c-Myc was increased, whereas association of Mad with Max appeared to be decreased. The amounts of each of YY1, c-Myc, Max, and Mad proteins synthesized in cells were not altered by HHV-6 infection. These data indicate that the decreased association of YY1 with c-Myc that is caused by impaired interaction in the c-Myc/Max/Mad network results in increased binding activity of YY1 to the CXCR4 promoter, mediating down-regulation of CXCR4 production in HHV-6-infected cells.


Human herpesvirus (HHV) 3–6 is a T-lymphotropic virus that was first isolated from patients with lymphoproliferative disorders and AIDS (1) and is now well known as a causative agent of exanthem subitum (2). It has also been established that reactivation of HHV-6 causes various clinical manifestations, including lymphadenitis, pneumonitis, hepatitis, meningoencephalitis, infectious mononucleosis-like disease, hemothagocytic syndrome, and hypersensitivity syndrome (3–6). HHV-6 isolates are divided into two subgroups, HHV-6A and HHV-6B, on the basis of their tropism for certain cell lines, reactivities with mAbs and HHV-6-specific T lymphocyte clones, and restriction enzyme cleavage patterns (7–9). The interaction between HHV-6 and HIV-1 is interesting because HHV-6 reactivation frequently occurs in patients with HIV-1 infection and HHV-6 and HIV-1 can coinfect CD4+ T lymphocytes, resulting in trans-activation of the HIV-1 long terminal repeat (LTR) and cell death (10–12).

It has been reported that various alterations of surface molecule expression of lymphocytes are induced by HHV-6 infection; that is, the expression level of CD3/TCR complex markedly decreases (13, 14) and de novo expression of CD4 is induced in CD4+ T lymphocytes and NK cells after infection with HHV-6A (15–17). These alterations of surface molecule expression result in dysfunc-

tion of T lymphocytes and susceptibility to HIV-1 infection of CD4+ lymphocytes (13–17). In addition to these findings, we have recently reported that the expression level of surface CXC chemokine receptor (CXCR) 4, which is a CXCR and a coreceptor for X4 HIV-1, markedly declines after infection with HHV-6A as well as HHV-6B (18). Down-regulation of CXCR4 has been reported also in HHV-7-infected cells by us and other investigators (18, 19). Down-regulation of CXCR4 resulted in impaired chemotaxis and a decreased level of elevation of the intracellular Ca2+ concentration in response to binding of the CXCR4 ligand, stromal cell-derived factor-1. Northern blot analysis of mRNAs extracted from HHV-6A- and HHV-6B-infected CD4+ T lymphocytes demonstrated a markedly decreased level of CXCR4 gene transcription compared with that in mock-infected cells, but the posttranscriptional stability was not significantly altered (18). These data indicate that down-regulation of CXCR4 in CD4+ T lymphocytes is induced by HHV-6 infection at the transcriptional level.

Understanding the mechanisms of down-regulation of CXCR4 would appear to be important, because manipulation of CXCR4 expression may lead to the development of novel means for protection against HIV infection. Recently, the structure of the promoter for the CXCR4 gene has been identified (20–22); this finding led us to study the mechanisms of transcriptional down-regulation of CXCR4 induced by HHV-6 infection. Our results demonstrated that impaired association between c-Myc, Max, and Mad results in increased DNA binding activity of YY1, which is a repressor of the CXCR4 promoter, in HHV-6-infected cells. On the basis of these findings, the significance of transcriptional down-regulation of this HIV-1 coreceptor, CXCR4, induced by HHV-6 infection is discussed.
lines, JJHAN and MT-4, were cultured in RPMI 1640 medium supplemented with 10% FCS then infected with HHV-6A and HHV-6B, respectively, at an approximate multiplicity of infection of 1.5% tissue culture infectious doses. All 9 T lymphocytes (15) and HHV-6B-infected and uninfected cells were cultured in a 5% CO2 incubator at 37°C until the cytopathic effect became detectable. Maximal cytopathic effect was usually detected after 4 days of virus inoculation.

**Flow cytometric analysis**

Expression of cell surface CXCR4 was examined by flow cytometric analysis using PE-conjugated anti-CXCR4 mAb (12G5; PharMingen, San Diego, CA). Cells to be used as unstained negative controls for CXCR4 were incubated with control PE-conjugated mouse monoclonal IgG (PharMingen).

**Preparation of cell nuclear extracts and EMSA**

The cells were washed with cold PBS and centrifuged. The cell pellet was then resuspended in 400 μl of cold lysis buffer (10 mM HEPES, pH 7.9, 0.1 mM EDTA, 1.0 mM PMSF, 0.2 mM Na3VO4, and 0.5% Nonidet P-40) by gently pipetting, and incubated on ice for 15 min. The centrifuge tube was then vortexed vigorously for 10 s and spun for 30 s. The nuclear pellet was suspended in 100 μl of cold protein extraction buffer (10 mM HEPES, pH 7.9, 400 mM NaCl, 1.0 mM EDTA, 1.0 mM PMSF, 0.2 mM Na3VO4, and 10% glycerol), vigorously vortexed for 15 min at 4°C, and centrifuged at 12,000 × g for 5 min at 4°C. The supernatant (nuclear extracts) was used as described above. The YY1 element (5'-TACGGAGGTAGCAAGGACCAGG 3'-3') from the promoter region of the CXCR4 gene was used as a probe. The annealed oligonucleotides were labeled by filling in their overhanging ends with the Klenow fragment in the presence of [α-32P]dCTP (3000 Ci/mol; Amersham Pharmacia Biotech, Buckinghamshire, U.K.). The labeled DNA fragment was incubated in a 40-μl final volume of reaction buffer (20 mM HEPES, pH 7.9, 50 mM KCl, 1 mM EDTA, 12% glycerol, 1 mM DTT, 2.5 μg poly(dI-dC) and 8 μg nuclear extract protein). After 20 min of incubation at room temperature, the sample was subjected to 4% PAGE in 0.5× TBE at 50 V, transferred to nitrocellulose membranes, and were blocked with 5% nonfat milk in TBS-T. The filters were incubated with mouse anti-Mad 1 Ab (B-12; Santa Cruz Biotechnology), and the c-Myc/Max complex was detected by immunoprecipitation using mouse anti-Mad 1 Ab (B-5; Santa Cruz Biotechnology). Similarly, the c-Myc/Max complex was detected by immunoprecipitation using mouse anti-MdM 2 Ab (B-22; Santa Cruz Biotechnology), and immunoblotting was performed with rabbit anti-Max Ab (C-12; Santa Cruz Biotechnology). The Max/Mad complex was detected by immunoprecipitation using mouse anti-MdM 2 Ab (B-5; Santa Cruz Biotechnology), and immunoblotting was performed with rabbit anti-Max Ab (C-12; Santa Cruz Biotechnology). The Western blot analysis alone, 30 μg of the whole cell lysates was subjected to 10% SDS-PAGE, and the following methods were used as the same described above. Goat anti-human CXCR4 Ab (C-20; Santa Cruz Biotechnology) and rabbit anti-GAPDH Ab (Trevesgen, Gaithersburg, MD) were used for this assay.

**Results**

Transcriptional down-regulation of CXCR4 in CD4+ T cell lines by HHV-6 infection

We previously reported that down-regulation of CXCR4 is induced by HHV-6A and HHV-6B infection in peripheral blood CD4+ T lymphocytes. As shown in Fig. 1A, down-regulation of surface CXCR4 was also detected in HHV-6A-infected JJHAN and HHV-6B-infected MT-4 cell lines. Kinetics studies showed that down-regulation of surface CXCR4 in HHV-6-infected cells was first detectable 2 days after virus inoculation and became maximal at day 4 of infection (data not shown). As we reported previously with regard to HHV-6-infected peripheral blood CD4+ T lymphocytes (18), the level of mRNA for CXCR4 was markedly decreased in CD4+ T cell lines after infection with HHV-6A and HHV-6B (Fig. 1B). To further confirm that down-regulation of CXCR4 in HHV-6-infected cells is induced at the transcriptional level and is not due to internalization of surface CXCR4 into the cytoplasm, Western blot analysis using whole cell lysates was performed. As shown in Fig. 1C, the expression level of CXCR4 protein in CD4+ T cell lines declined markedly after infection with HHV-6A and HHV-6B. These data confirm our previous finding that down-regulation of CXCR4 in HHV-6-infected cells is induced at the transcriptional level and suggest that transcriptional
down-regulation of CXCR4 is induced ubiquitously by HHV-6 infection in various types of cells.

**CXCR4 promoter activity in HHV-6- and mock-infected cells**

To identify the promoter region involved in the down-regulation of CXCR4 in HHV-6-infected cells, a series of 5’ flanking sequences were amplified by PCR and linked to the luciferase reporter gene. A series of the constructs formed with progressive 5’ deletions of the CXCR4 promoter sequence was generated spanning bases -2334/+76, -2313/+76, -2186/+76, -2124/+76, -181/+76, -76/+76, and -56/+76. Each of the constructs was transfected into HHV-6- and mock-infected cells, and luciferase activity was determined. As reported previously (20), a YY1 binding site at around -2320 relative to the transcription start site appeared to be involved in the negative regulation of CXCR4 transcription in mock-infected cells (Fig. 2). The degree of repression of CXCR4 promoter activity mediated by this YY1 binding site was significantly higher in HHV-6-infected cells than in mock-infected cells, suggesting that YY1 inhibits CXCR4 promoter activity through its binding to the CXCR4 promoter.

**Down-regulation of CXCR4 induced by overexpression of YY1**

To examine the role of YY1 in down-regulation of CXCR4, T cell lines, JJHAN and MT-4, were transduced with a YY1 expression plasmid and a control plasmid. A significantly increased level of YY1 protein expression was detected in cells transduced with the YY1 expression vector compared with cells transduced with the control vector and untreated cells (data not shown). As shown in Fig. 3, overexpression of YY1 resulted in significant reduction of cell surface CXCR4 expression. This finding confirmed the repressor activity of YY1 on the CXCR4 promoter.

**Differential DNA binding activity of YY1 in HHV-6- and mock-infected cells**

To compare the binding activity of YY1 to the CXCR4 promoter in HHV-6- and mock-infected cells, EMSA was performed using a YY1-binding probe. As shown in Fig. 4, the density of the single band differed significantly between HHV-6- and mock-infected cells. This DNA-binding protein was identified as YY1, because the band was completely eliminated by excess unlabeled YY1 binding competitor, and addition of anti-YY1 Ab supershifted this complex. Therefore, it appeared that the binding activity of YY1 to

**FIGURE 1.** Expression of CXCR4 in HHV-6A-infected, HHV-6B-infected, and mock-infected cells. A, Flow cytometric analysis of surface CXCR4 expression. The stainings with negative control Ab are shown as open histograms. B, Northern blot analysis of mRNA for CXCR4. Samples of total cellular RNA were hybridized with a 32P-labeled CXCR4 cDNA probe and a GAPDH cDNA probe. C, Western blot analysis of CXCR4 protein. Whole cell extracts were subjected to Western blotting using goat anti-CXCR4 Ab and mouse anti-GAPDH Ab. The results shown are representative of triplicate experiments.

**FIGURE 2.** Deletion analysis of CXCR4 promoter activity. JJHAN cells were transfected with luciferase expression vectors containing 5’ deletions of the CXCR4 promoter sequence and infected with HHV-6A or treated with mock-infected culture supernatant. Cells were harvested and lysed at 48 h postinfection, and luciferase activity was determined. The amounts of cell lysates were standardized by sea-pancy luciferase activity in the lysates. Results are mean ± SD of four independent experiments.

**FIGURE 3.** Down-regulation of CXCR4 expression by overexpression of YY1. CXCR4 expression in JJHAN and MT-4 cells that were transfected with pCMV-YY1 or pCMV was examined by flow cytometric analysis.
the CXCR4 promoter was increased significantly in HHV-6-infected cells compared with the binding activity in mock-infected cells, suggesting that increased binding activity of YY1 to the promoter results in down-regulation of CXCR4.

Association between YY1, c-Myc, Max, and Mad in HHV-6- and mock-infected cells

Previous in vitro and in vivo studies revealed that c-Myc inhibits YY1 activity by its direct association with YY1 (25–27). This finding conversely suggests that decreased association of c-Myc with YY1 would result in increased YY1 activity and lead us to study the alteration in association of c-Myc with YY1 in HHV-6-infected cells. The whole cell extracts were immunoprecipitated with anti-YY1 Ab, and the amounts of c-Myc in the immunocomplexes were determined by Western blot analysis with anti-c-Myc Ab. As shown in Fig. 5, the levels of c-Myc associated with YY1 were significantly decreased in HHV-6A-infected JJHAN cells and HHV-6B-infected MT-4 cells, compared with mock-infected JJHAN cells and mock-infected MT-4 cells, respectively. These findings support our hypothesis that the increased binding activity of YY1 to the CXCR4 promoter in HHV-6-infected cells might be a result of decreased association of c-Myc with YY1.

We further investigated the mechanisms of the decreased association of c-Myc with YY1 in HHV-6-infected cells. First, to examine whether c-Myc is capable of regulating the CXCR4 promoter activity, the expression vector of c-Myc was cotransfected with CXCR4 promoter luciferase reporter constructs. As shown in Fig. 6, overexpression of c-Myc increased the CXCR4 promoter activity in JJHAN cells. This finding strongly suggests that YY1-mediated down-regulation of CXCR4 is inhibited by c-Myc.

c-Myc is known to exert its activity by heterodimerization with its partner protein, Max. In contrast, Max also heterodimerizes with Mad to antagonize c-Myc. On the basis of these findings, we investigated the association of Max with c-Myc and that of Mad with Max. First, the whole cell extracts were immunoprecipitated with anti-c-Myc Ab, and the amounts of Max in the immunocomplexes were determined by Western blotting with anti-Max Ab. As shown in Fig. 7A, the level of Max associated with c-Myc in HHV-6-infected cells was higher than that in mock-infected cells (Fig. 7A). Next, the whole cell extracts were immunoprecipitated with anti-Max Ab, and the amounts of Mad in the immunocomplexes were determined by Western blotting with anti-Mad Ab. As shown in Fig. 7B, the level of Mad heterodimerized with Max was significantly decreased in HHV-6-infected cells compared with the level in mock-infected cells. The same results were obtained from triplicate runs of each immunoprecipitation assay.

Syntheses of YY1, c-Myc, Max, and Mad proteins in HHV-6- and mock-infected cells

To determine whether the altered associations among YY1, c-Myc, Max, and Mad in HHV-6-infected cells are induced by the impaired protein synthesis, we performed Western blot analysis using whole cell lysates and Abs against these transcriptional factors. As shown in Fig. 8, the levels of synthesis of each of YY1, c-Myc, Max, and Mad protein appeared to be unchanged after infection with HHV-6. These findings strongly suggest that HHV-6 infection does not affect the protein syntheses of YY1, c-Myc, Max, or Mad, but induces altered binding associations between these transcription factors.

FIGURE 5. In vivo association of c-Myc with YY1 in mock- and HHV-6-infected cells. Whole cell extracts from cells were used for immunoprecipitation with anti-YY1 Ab. The precipitates were subjected to 10% SDS-PAGE followed by Western blotting with anti-c-Myc Ab. The results shown are representative of triplicate experiments.

FIGURE 6. Increased CXCR4 promoter activity by overexpression of c-Myc. JJHAN cells were transiently cotransfected with the luciferase expression vector containing the CXCR4 promoter sequence including the YY1-binding region spanning the region from -334 to +76 relative to the transcription start site, and pcDNA3-c-myc or pcDNA3. Cells were harvested and lysed at 48 h after transfection, and luciferase activity was determined. The amounts of cell lysates were standardized by sea-pancy luciferase activity in the lysates. Results are mean ± SD of four independent experiments.

FIGURE 4. EMSA with a YY1 oligonucleotide. EMSA was performed with a 32P-labeled YY1 probe using mock-infected (lanes 1, 3, 5, 7, and 9) and HHV-6-infected cell nuclear extracts (lanes 2, 4, 6, 8, and 10). Competitors of unlabeled oligonucleotides (lanes 3–6), anti-YY1 Ab (lanes 7 and 8), or rabbit polyclonal IgG (lanes 9 and 10) were added to the reaction mixture.

FIGURE 6. Increased CXCR4 promoter activity by overexpression of c-Myc. JJHAN cells were transiently cotransfected with the luciferase expression vector containing the CXCR4 promoter sequence including the YY1-binding region spanning the region from -334 to +76 relative to the transcription start site, and pcDNA3-c-myc or pcDNA3. Cells were harvested and lysed at 48 h after transfection, and luciferase activity was determined. The amounts of cell lysates were standardized by sea-pancy luciferase activity in the lysates. Results are mean ± SD of four independent experiments.
down-regulation of CXCR4 is also induced in the CD4
HHV-6 infection (18). In this study, we obtained evidence that
CXCR4 transcription.

representative of triplicate experiments.

FIGURE 7. In vivo associations of Max with c-Myc and Mad with Max in mock- and HHV-6-infected cells. A, Whole cell extracts from cells were used for immunoprecipitation with anti-c-Myc Ab. The precipitates were subjected to 10% SDS-PAGE followed by Western blotting with anti-Max Ab. B, Whole cell extracts from cells were used for immunoprecipitation with anti-Max Ab. The precipitates were subjected to 10% SDS-PAGE followed by Western blotting with anti-Mad Ab. The results shown are representative of triplicate experiments.

Mechanisms of transcriptional down-regulation of CXCR4 in HHV-6-infected cells

On the basis of these data, we summarized the mechanisms of down-regulation of CXCR4 in HHV-6-infected cells (Fig. 9). That is, HHV-6 infection mediates decreased association of Max with Mad and increased association of Max with c-Myc. These alterations result in decreased levels of the YY1/c-Myc complex and consequent increased binding activity of YY1, a negative regulator of CXCR4, to the CXCR4 promoter, resulting in inhibition of CXCR4 transcription.

Discussion

We have recently reported that transcriptional down-regulation of CXCR4 is induced in peripheral blood CD4+ T lymphocytes by HHV-6 infection (18). In this study, we obtained evidence that down-regulation of CXCR4 is also induced in the CD4+ T cell lines, JIHAN and MT-4, by infection with HHV-6A and HHV-6B, respectively, and further investigated the mechanisms of transcriptional down-regulation of CXCR4 induced by HHV-6 infection. The data obtained through the series of these experiments are as follows. First, on the basis of the data obtained from luciferase assays, the binding site of YY1 (which is considered to be a repressor of CXCR4 transcription) around −320 relative to the transcriptional start site appeared to be the important promoter region for HHV-6-induced CXCR4 down-regulation. This was confirmed by evidence that overexpression of YY1 in CD4+ T cell lines resulted in down-regulation of CXCR4 expression. Second, the binding activity of YY1 to the CXCR4 promoter was significantly increased in HHV-6-infected cells, compared with the activity in mock-infected cells. Third, immunoprecipitation assays revealed that the association of c-Myc with YY1 was decreased, that of Max with c-Myc increased, and that of Mad with Max decreased. These findings suggest that HHV-6 infection affects the network of c-Myc, Max, and Mad, resulting in the decreased association of c-Myc with YY1 and increased binding activity of free YY1 to the CXCR4 promoter. These data provide the first evidence that virus infection induces down-regulation of CXCR4, which is a chemokine receptor and a coreceptor for X4 HIV-1, through impaired association of the negative transcription factor YY1 with c-Myc.

YY1 is a zinc finger transcription factor that is ubiquitously expressed and highly conserved among mammalian species (25). Depending on the promoter analyzed and on the cellular context, YY1 either stimulates or represses gene transcription. In addition, it has also been implicated in initiator function. In this study, a YY1 binding site around −320 relative to the CXCR4 transcription start site appeared to be important for suppression of CXCR4 promoter activity. Transfection of the YY1 expression vector into CD4+ T cell lines resulted in a reduction in the level of surface CXCR4 expression, supporting the previous report by Moriuchi et al. that YY1 is a repressor of CXCR4 transcription (28). The binding activity of YY1 to CXCR4 promoter was significantly increased in HHV-6-infected cells compared with mock-infected cells, strongly suggesting that increased binding activity of YY1 to the CXCR4 promoter is the main cause of CXCR4 down-regulation induced by HHV-6 infection. It has been reported that YY1 is physically associated with c-Myc in vitro and in vivo and that YY1 activity is inhibited by this interaction (25–27); that is, overexpression of c-Myc inhibits both the transcriptional activation and
repression of YY1 in a dose-dependent manner (28). Conversely, reduction of the c-Myc level induces an increase in the level of free YY1, resulting in increased DNA-binding activity of YY1 (27). These previous findings were confirmed by our present study in which overexpression of c-Myc increased the activity of the CXCR4 promoter spanning a YY1 binding site. The present immunoprecipitation assays demonstrated that the association of c-Myc with YY1 decreased after HHV-6 infection. Because the overall protein levels of YY1 and c-Myc in CD4+ T lymphocytes remained unchanged after infection with HHV-6, impaired association of YY1 with c-Myc might result in an increase in the level of free YY1 that induces transcriptional down-regulation of CXCR4 in HHV-6-infected cells.

The transcription factor c-Myc does not homodimerize but heterodimerizes with a partner protein, Max, to regulate gene expression (29, 30). The complex of c-Myc/Max is capable of recognizing the core E box element, 5′-CACGTG-3′. In contrast, Max also heterodimerizes with the Mad family proteins to repress transcription and antagonize c-Myc (31–34). All of the functional domains of c-Myc, Max, and Mad contain the basic helix-loop-helix leucine zipper domain, YY1 (35). In this study, it was found that the association of Mad with Max significantly decreased in HHV-6-infected cells. In addition, the association of Max with c-Myc appeared to increase after HHV-6 infection. The expression levels of c-Myc, Max, and Mad proteins remained unchanged in HHV-6-infected cells. Taken together, these observations strongly suggest that HHV-6 infection of CD4+ T lymphocytes affects the network of c-Myc, Max, and Mad, resulting in the augmentation of c-Myc-Max heterodimerization. Moreover, the increased association of c-Myc with Max may result in the decreased association of YY1 with c-Myc, as discussed above. It is well known that c-Myc expression affects various cellular functions, including apoptosis (36, 37). We previously reported that HHV-6 infection renders CD4+ T lymphocytes susceptible to apoptosis (38), suggesting that the increased association of c-Myc with Max may be one of the causes of CD4+ T lymphocyte apoptosis mediated by HHV-6 infection.

Because CXCR4 is an important coreceptor for HIV-1, this study seems to be important for understanding the pathogenesis of AIDS. It has recently been reported that Tax protein from human T-tropic retrovirus type I activates the CXCR4 promoter (39), and that influenza virus also up-regulates CXCR4 expression at a transcriptional level (40). These findings suggest that infectious agents such as human T-tropic retrovirus type I and influenza virus may contribute to disease progression in HIV-1-infected individuals by modulating HIV-1 coreceptor expression. Previous studies have demonstrated that HHV-6 can coinfected with HIV-1 and trans-activate the LTR of HIV-1 (10–12). In addition, it has been reported that CD4 expression is induced by HHV-6 infection of CD4+ lymphocytes (15–17). On the basis of these findings, HHV-6 has also been considered a cofactor for progression of HIV-1 infection. However, our present data provide a possibility opposite to that proposed previously; that is, CXCR4 down-regulation mediated by HHV-6 may render CD4+ T lymphocytes resistant to infection with X4 HIV-1. This study also provides a new concept for developing protection against HIV-1 infection. In addition to its repressor function on CXCR4 transcription, YY1 has been reported to repress HIV-1 LTR transcription activity (41, 42). Because overexpression of YY1 did not affect the main characteristics of cells, including morphology, cell growth, and intracellular signaling through TCR (data not shown), the potential exists for gene therapy of AIDS focusing on cellular transcription factors such as YY1. In this study, we could not identify the components of HHV-6 that induce the impairment of the c-Myc/Max/Mad network. The mechanisms by which HHV-6 mediates the altered interaction between these transcription factors should be clarified by further studies. This information should shed light on our understanding of the detailed pathogenesis of HHV-6 infection and also provide a novel strategy for protection against HIV infection.

Acknowledgments

We thank Dr. Thomas Shenk for providing the YY1 expression vector. We also thank Drs. Hiroyuki Morishita, Masako Morishita, and Nobuaki Hatta for their helpful suggestions.

References


