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HIV Envelope Protein Inhibits MHC Class I Presentation of a Cytomegalovirus Protective Epitope

Daniel López,* Yolanda Samino,* Ulrich H. Koszinowski, † and Margarita Del Val2*

CTL recognize peptides that derive from viral protein Ags by proteolytic processing and are presented by MHC class I molecules. In this study we tested whether coexpression of viral Ags in the same cell leads to competition between them. To this end, two Ld-restricted epitopes derived from HIV-I envelope gp160 (ENV) and from CMV pp89 phosphoprotein were coexpressed. HIV ENV strain IIB, but not MN variant, impaired recognition by specific CTL of CMV pp89 epitope 9pp89. Susceptibility to inhibition after ENV coexpression was inversely related to the amount of antigenic 9pp89 peptide processed from different antigenic constructs. In line with it, competition decreased the yield of naturally processed antigenic 9pp89 peptide bound to MHC class I molecules in coinfected cells. Also, point mutants of the presenting MHC class I molecule differed in their competition pattern. Collectively, the data imply that competition operates at the step of MHC-peptide complex assembly or stabilization. We conclude that, although not the rule, in certain combinations there is interference between different Ags expressed in the same cell and presented by the same MHC class I allele. These studies have implications for vaccine development and for understanding immunodominance. The Journal of Immunology, 2001, 167: 4238–4244.

Viruses encode a high number of potential epitopes that can be presented by MHC class I molecules. Analysis of viral epitopes that are recognized in the infected host usually shows that the response to one epitope is much higher than to other potential epitopes, which are either not or only marginally recognized. Thus, one usually finds immunodominant and cryptic epitopes. If by mutation the pathogen loses the immunodominant epitope(s), some previously cryptic epitopes may become immunodominant (1, 2). This indicates that it is not intrinsic properties of these previously cryptic epitopes that precluded their efficient presentation to T lymphocytes. Rather, factors external to the epitope itself should account for it. It has been hypothesized that the presence of a very strong epitope renders cryptic another one of regular strength (2, 3) because of competition between them, be it at the level of the infected cell, the presenting cell, or the CD8+ T lymphocyte.

We are interested in studying whether the coexpression of several Ags in the same cell compromises the efficiency of presentation to CD8+-specific T cells, particularly when they are restricted by the same MHC class I molecule. The endogenous pathway of viral Ag presentation to CTL comprises several steps, including proteolytic processing by proteasomes or other enzymes (4–7), peptide transport to the endoplasmic reticulum (ER)3 by TAP, assembly of the peptide/MHC complex, and migration to the cell membrane. It is possible that different Ags may compete with each other at any of these stages. This question was addressed in a mouse model by studying the interference between two Ags recognized by CD8+ CTL, both presented by the murine MHC class I molecule Ld (8, 9). One is derived from HIV-I strain IIB, the immunodominant determinant 31RGPRAFVT127 of the envelope gp160 (ENV), which is also presented by various murine (Dd (10), H-2d, H-2b, and H-2a (11)), and human class I molecules (HLA-A2 (12), -A11 (13), -A3 (14), and -B27 (15)). The second epitope is derived from murine CMV, corresponds to the immunodominant 168YPHFMPNLT176 nonamer of the nuclear phosphoprotein pp89, and can elicit CD8+ T lymphocytes that protect against lethal murine CMV infection (16–18). This report shows that HIV ENV interfered with presentation of CMV pp89 epitope (9pp89) to CTL, and that this occurred at the level of processed peptides bound to MHC class I molecules in the coinfected cells.

Materials and Methods

Mice

BALB/c mice (H-2d haplotype) were bred in our colony.

Cell lines

All cell lines were cultured in IMDM supplemented with 10% FCS and 5 × 10−5 M 2-ME. Generation of site-directed Ld mutants and their transfection into murine L fibroblasts is described elsewhere (19, 20). Transfectants are named according to the new amino acid substituting for the native amino acid at the indicated residue number. Accordingly, transfected R144K/R145H was renamed as Ld107W116Y155H157K. T2 cells transfected with Ld have been described (21).

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Synthetic peptides

Peptides were synthesized in a peptide synthesizer (model 431A; Applied Biosystems, Foster City, CA), purified, and found homogeneous by reversed-phase HPLC. The sequences are as follows: pp989, YPHFMPPTNL; 10ENV, RGPGRAFYTI; 9ENV, GPGRAFYTI; 9ENV-MN, GPGRAFYTI.

Recombinant vaccinia viruses (rVV)

Generation of rVV-eN-A9pp89A and rVV-HBe viruses has been described previously (22). The former encodes the murine CMV 9pp89 immunodominant epitope flanked by five alanines and inserted into the amino terminus of the secretory core protein of hepatitis B virus (HBe). rVV-εC-10env encodes the HIV-1 strain IIIB ENV 318–327 epitope at the carboxyl end of HBe (7). The rVV-sN-9pp89S recombinant was generated similarly (22), and the sequence at the N-terminal insertion site is ... indi-GYPHMPPTNL6dp... where the lower-case letters indicate the native HBe carrier protein N-terminal sequence. As opposed to the other HBe-based constructs, this one contains the influenza virus hemagglutinin signal in place of the native HBe signal sequence, and the 9pp89 epitope is not flanked by alanines. rVV-ENV-IIBb virus (rSC25) encodes ENV envelope glycoprotein from the strain IIB of HIV-1 (23). rVV-ENV-MN encodes ENV from strain MN of HIV-1 (10), which contains the homologous epitope. 9pp89 is presented by Dd (10). rVV-encoded proteins ankled by alanines. rVV-ENV-IIIB virus (vSC25) encodes ENV envelope glycoprotein from the strain IIB of HIV-1 (23). rVV-ENV-MN encodes ENV from strain MN of HIV-1 (10), which contains the homologous epitope. 9pp89 is presented by Dd (10). rVV-encoded proteins

MHC/peptide stability assays

T2Ld cells were incubated overnight at 26°C, washed, and incubated for 2 h at 37°C in PBS containing 0.1% BSA and 500 µM of the different peptides. A control without peptide was also included. After washing, the cells were resuspended in the same buffer (time point 0 h) and were further incubated at 37°C. Aliquots removed at different time points were stained with mAb 30-5-7, which recognizes Ld bound to peptide (24), and FITC-labeled goat anti-mouse Ab, or with the second Ab alone. Analysis of fixed cells was performed in a FACScan (BD Biosciences, Mountain View, CA). Fluorescence index was calculated at each time point as the ratio of mean linear fluorescence of the sample to that of the control incubated without peptide.

Results

Interference with Ag presentation

Coinfection experiments were performed with rVV that express either HIV-1 ENV or CMV pp989 optimal 9 mer, named pp989, in an optimal chimeric peptide context (22). Coinfection of rVV-eN-A9pp89A together with an excess of the control virus rVV-HBe did not affect the recognition of infected Ld fibroblasts by CMV-specific CTL (Fig. 1A). Vaccinia codes for some unidentified Ags presented by Ld (9), which by their nature and amount apparently do not prevent pp989 Ag processing and presentation by Ld (18), nor that of many other Ags (25). These results show that this is also true even when vaccinia Ags are expressed in 5-fold excess. Coinfection experiments with rVV-ENV-IIBb, however, practically abolished recognition of pp989 (Fig. 1A), with an average inhibition of 73 ± 13% (n = 10). Coinfection experiments in the macrophagic cell line J774 led to similar specific inhibition of pp989 presentation caused by coexpression of ENV (83 ± 6%, n = 5), whereas the negative control WR did not cause any interference (5%). These data showed that although not the rule, in certain combinations there is interference between different Ags expressed in the same cell and presented by the same MHC class I allele.

Competition experiments with exogenously added synthetic peptides showed that incubation with an excess of HIV ENV 318–

FIGURE 1. Cytolytic assays with coinfected rVV. Infection of Ld fibroblast target cells with rVV-eN-A9pp89A (named Ag) at moi 3 and with the following competing viruses at moi 15: rVV-ENV-IIBb, rVV-εC-10env, rVV-ENV-MN, and rVV-HBe. Ld cells were coinfected with the corresponding viruses overnight and were then used as target cells for recognition by pp989-specific CTL (Fig. 1A). Vaccinia codes for some unidentified Ags presented by Ld (9), which by their nature and amount apparently do not prevent pp989 Ag processing and presentation by Ld (18), nor that of many other Ags (25). These results show that this is also true even when vaccinia Ags are expressed in 5-fold excess. Coinfection experiments with rVV-ENV-IIBb, however, practically abolished recognition of pp989 (Fig. 1A), with an average inhibition of 73 ± 13% (n = 10). Coinfection experiments in the macrophagic cell line J774 led to similar specific inhibition of pp989 presentation caused by coexpression of ENV (83 ± 6%, n = 5), whereas the negative control WR did not cause any interference (5%). These data showed that although not the rule, in certain combinations there is interference between different Ags expressed in the same cell and presented by the same MHC class I allele.

Competition experiments with exogenously added synthetic peptides showed that incubation with an excess of HIV ENV 318–

Isolation of naturally processed peptides

Transfectants were infected in parallel with the different mixes of rVV at the indicated multiplicity of infection (moi), and 16 h later, naturally processed peptides were extracted from whole cells with trifluoroacetic acid and were purified essentially as previously described (22). Instead of gel filtration, Macrosep 3K centrifugal concentrators (Pall Filtron, Nor-
327 epitope led to inhibition of recognition by CTL of 9pp89-peptide-loaded L/L\(^d\) fibroblasts, indicating that ENV peptides can prevent MHC-restricted presentation of exogenous 9pp89 (Fig. 2).

To investigate whether the interference observed in infected cells was caused by the L\(^d\)-restricted epitope of ENV-IIIB, a rVV was constructed that expressed this 318–327 epitope in a different protein context, that of the secretory HBe protein. Fig. 1B shows that the rVV-ec-10env virus also interfered with 9pp89 Ag presentation, although less efficiently than ENV (35 ± 13%, \(n = 10\)). In part, this may be due to a lower efficacy of ENV epitope processing and presentation from the former construct, because lysis by ENV epitope-specific CTL of L/L\(^d\) cells revealed a stronger recognition of full-length ENV than of the epitope construct (data not shown). Conversely, when the natural MN variant of ENV that differs at the epitope sequence was used as coinfecting virus, no inhibition of CMV epitope presentation was detected (Fig. 1C).

Again, a control WR virus with a different wild-type background did not interfere either. The MN variant, as well as the synthetic peptide mimicking its sequence in the epitope area, was not recognized by ENV-IIIB-specific CTL in L/L\(^d\) cells either (data not shown). Altogether, these results indicate that the L\(^d\)-restricted ENV epitope alone is able to partially interfere.

As a control, the effect of coinfection with the different viruses on the level of expression of the antigenic protein eN-A9pp89A was checked by Western blot. As shown in Fig. 3 (upper panel), although coinfection with a 5-fold excess of another rVV somehow decreased the level of eN-A9pp89A protein, this happened to a similar degree with the interfering ENV-IIIB and with wild-type WR. In addition, although coinfection with rVV-ENV-MN strongly affected eN-A9pp89A protein expression (lane 4), this was not sufficient to affect specific recognition of infected cells by CTL (Fig. 1C). A similar reduction in total protein level after coinfection was detected when protein expression was analyzed with an ENV-IIIB-specific mAb (Fig. 3, lower panel). Thus, in conclusion, ENV interfered with CMV 9pp89 Ag presentation and this could not be explained by a selective reduction in intracellular levels of the antigenic protein.

**Lack of antagonism between CMV 9pp89 and HIV 9ENV synthetic peptides**

The findings described above are compatible with two situations. The two full-length Ags or peptides derived from them may compete intracellularly in the processing and presentation pathway. Alternatively, peptides derived from both epitopes may bind separately to MHC, and ENV complexes may antagonize (26) pp89-specific CTL at the cell surface. The latter possibility was simulated with synthetic peptides. Uninfected cells loaded with 9ENV were used as cold inhibitors of \(^{51}\)Cr-labeled 9pp89-loaded target cells, and were found not to block CTL recognition of 9pp89 (Fig. 4). As a positive control, when both cold and labeled cells were preloaded with 9pp89, inhibition of lysis was observed. Altogether, these results indicated absence of antagonism between both epitopes, suggesting that interference occurred within the infected cell.

**Competition quantitatively affects the yield of naturally processed peptides**

To confirm that the interference between both Ags occurred intracellularly, the amount of naturally processed peptides extracted from infected cells was assessed. Peptides that coelute in fraction

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**FIGURE 2.** Competition by ENV synthetic peptides for 9pp89 exogenous presentation. Cytolysis experiments were conducted using \(1 \times 10^{-10}\) M 9pp89 and different 10ENV (filled bars) or 9ENV (open bars) concentrations. Each mix of 9pp89 and an ENV peptide was preincubated with L/L\(^d\) target cells before addition of anti-pp89 CTL. A 9pp89 concentration of \(10^{-10}\) M was chosen because it was the lowest one that still gave maximal CTL recognition in the absence of ENV peptides.

**FIGURE 3.** Western blot analysis of coinfected cells. L/L\(^d\) cells were infected with rVV-eN-A9pp89A alone (lane 1) or coinfected with rVV-ENV-IIIB (lane 2), with rVV-WR (lane 3) or with rVV-ENV-MN (lane 4). Cells in lane 5 were infected with rVV-ENV-IIIB alone. Reactivity with an HBe/HBe-specific serum to reveal eN-A9pp89A is shown above, and detection with an HIV strain H1B ENV epitope-specific mAb is shown below.

**FIGURE 4.** Cold target inhibition assays. Labeled (+) P815 target cells were preincubated with 9pp89 (•). As unlabeled “cold” target cells, P815 were used that were preincubated with either 9ENV (○) or 9pp89 (■). P815 cells without peptide were used as negative control (▲). The cytolytic assay of the mixtures of labeled and cold targets was performed with pp89-specific CTL. Similar results as those shown for P815 cells were also obtained with L/L\(^d\) cells (data not shown).
31 with the synthetic 9pp89 and that constitute the major antigenic activity of the CMV protein in reversed-phase HPLC runs were analyzed. Serial dilution of this material allowed quantitation of 9pp89 obtained from coinfection experiments with the control rVV-HBe or with the rVV that expressed the ENV epitope (rVV-eC-10env) (Fig. 5). The data showed 3- to 10-fold less rVV-eN-A9pp89A-derived 9pp89 obtained from cells coinfected with ENV rVV than with control rVV-HBe. Such a decrease in the yield of endogenously processed 9pp89 peptide was previously found to severely impair induction of protective immunity to murine CMV (22). No antigenicity was recovered from infected cells lacking Ld (data not shown). Thus, inefficient Ag presentation in ENV epitope-expressing cells correlated with a lower amount of processed 9pp89 peptide bound to Ld. Collectively, these results suggested that Ag competition took place intracellularly before or at the step of peptide binding to Ld.

The degree of inhibition is inversely related to the amount of antigenic peptide

Because intracellular competition for Ag presentation correlated with lower amounts of naturally processed 9pp89 peptide, constructs that yield less processed 9pp89 should be easier to compete with. rVV-eN-A9pp89A and rVV-sN-9pp89S viruses express the immunodominant CMV epitope with different local flanking regions. Quantitation of naturally processed peptides from both chimeric proteins yielded 5- to 10-fold less 9pp89 peptide from rVV-sN-9pp89S (E. Luderer, M. Del Val, and U. H. Koszinowski, unpublished data), which correlated with target cell lysis. Fig. 6 shows coinfection followed by cytolysis using rVV-eC-10env as competing virus. The specific inhibition by rVV-eC-10env of rVV-sN-9pp89S (78 ± 14%; n = 3) was more prominent than that of rVV-eN-A9pp89A (35 ± 5%) at the same moi ratios (1:5, Ag: competitor). Thus, inhibition is stronger under conditions where less antigenic peptide is generated.

The reverse situation was also explored; namely, increasing the amount of naturally processed 9pp89 peptide by raising the moi of the Ag rVV-sN-9pp89S. When a 3-fold higher moi of rVV-sN-9pp89S was used, but the same Ag: competitor ratio was maintained, specific inhibition decreased from 78 to 43 ± 5% (n = 4; Fig. 6). This revealed that increasing amounts of antigenic peptide gradually reverse competition. These results also exclude a non-specific interference by vaccinia virus properties and support the Ag-specific nature of the interference.

Point mutations in the MHC class I molecule affect the competition pattern

If peptides would compete for binding to MHC molecules, then MHC mutants that affect the peptide groove and that selectively modulate binding of the antigenic peptide (20) or of the competitor should differ in their capacity to resist competition. Coinfection and cytolysis assays were performed using L cells transfected with different MHC class I molecule Ld mutants. Six transfectants, including L/Ld, from a panel of 11 MHC class I mutant cells (19, 20), were able to present rVV-eN-A9pp89A to CTLs and were tested for competition (Fig. 7). The results show that rVV-ENV-IIB efficiently inhibited 9pp89 presentation in all cases, whereas inhibition by rVV-eC-10env was only partial, as described above for L/Ld. Transfectants L/Ld107W116Y155H157K, L/Ld195I, and L/Ld144K145H (the last two not shown) exhibited a similar reaction pattern as Ld-expressing target cells. In these transfectants, the degree of inhibition by rVV-ENV was on average 2-fold higher than the inhibition caused by rVV-eC-10env. In contrast, the two transfectants L/Ld116Y and L/Ld107W116Y differed from the previous pattern. Both displayed a significantly lower percentage of specific inhibition with rVV-eC-10env virus as compared with rVV-ENV, by a factor of around 4 (Fig. 7). These data show that mutation of MHC class I molecules alters the competition hierarchy in cells that otherwise share the whole Ag processing and presentation machinery. Hence, interference appears to be the result of competition between different peptides for binding to Ld or mutants thereof. Therefore, competition probably operates at the step of MHC-peptide complex assembly or stabilization.

To assess the relative stability of the complexes of the MHC molecule with the different peptides, TAP-deficient T2 cells transfected with Ld were used. Fig. 8 shows that the stability of the surface complexes with the 9pp89 peptide or with the strain IIB 10ENV peptide was similar. Peptide 9ENV produced slightly less
Nevertheless bound to Ld, albeit with less stability. These results are compatible with the hypothesis that inhibition of 9pp89 peptide presentation is directly caused by the presence of processed ENV peptides at sites of peptide/MHC assembly.

**FIGURE 8.** Stability of MHC/peptide complexes. After loading of T2/Ld cells with the indicated peptides, these were washed away and the stability of the surface MHC/peptide complexes was estimated by staining the cells at different time points with the peptide-dependent Ld-specific 30-5-7 mAb, followed by flow cytometry. Peptides: 9pp89 (△), 10ENV from IIB (●), 9ENV from IIB (●●), and 9ENV-MN (■). Cells incubated without peptide had mean fluorescence intensities close to background fluorescence index of 2. Results are the mean of three different experiments.

**FIGURE 7.** Competition in different MHC class I transfectants. L cells transfected with Ld mutated in the indicated positions and amino acids were coinjected with rVV-eN-A9pp89A at moi 3 and the rVV indicated on the left as competing viruses at moi 15. They were then used as target cells. Lysis of cells coinjected with rVV-eN-A9pp89A and control rVV-HBe, which were used to calculate specific inhibition, were 24, 30, 25, 38, 25, and 35% for transfectants L/Ld107W116Y, L/Ld116Y, L/Ld107W116Y155H157K, L/Ld95I, L/Ld144K145H, and Ld, respectively. The column at the right indicates the ratio of the inhibition caused by ENV to that caused by eC-10env. The factor for the transfectants not shown was 2.8, 2.4, and 2.1 for L/Ld95I, L/Ld144K145H, and Ld, respectively.

stable complexes. The homologous 9 mer from the MN strain, for which no evidence of presentation by Ld has been reported, nevertheless bound to Ld, albeit with less stability. These results are compatible with the hypothesis that inhibition of 9pp89 peptide presentation is directly caused by the presence of processed ENV peptides at sites of peptide/MHC assembly.

**Discussion**

In this report we address the question of interference between simultaneously expressed antigenic epitopes. We demonstrate that coexpression of two epitopes, one derived from HIV-1 ENV IIIB, but not from MN, and the CMV 9pp89 epitope, decreases the presentation by MHC class I molecules of CMV 9pp89 to specific CD8+ CTL. This is probably caused by intracellular competition of processed Ags for binding to MHC class I molecules. To our knowledge, this is the first report that describes such a selective competition for peptide presentation caused by HIV-1 ENV protein.

The interference by the full-length ENV protein is higher than that by the Ld-restricted 318–327 epitope construct. Thus, beside the action of the epitope itself, a contribution of other unknown Ld-restricted epitopes or other properties of the ENV protein to inhibition appear likely. Interestingly, TAP-independent presentation of several HLA-restricted ENV epitopes has been described (27, 28), which can act simultaneously with the TAP-dependent classical presentation pathway. In our murine system, presentation of the 318–327 epitope from full-length ENV is TAP dependent (6), while it can follow both a TAP-dependent and a TAP-independent pathway from the chimeric protein (6, 7). Thus, additional ENV-derived peptides processed also in the secretory pathway may constitute an extra source of peptides that may compete with 9pp89 in our experiments. Notably, preferential and specific proteolytic cleavage of ENV protein occurs between residues 315 and 316, adjacent to the Ld-restricted epitope, as detected in several cell lines (29, 30) including the L cells used in our study (31). The long-time residence of ENV in the ER (28) would favor this cleavage. This may also explain the higher efficiency of recognition of the full-length ENV by ENV epitope-specific CTL. The described O-glycosylation of ENV at this epitope sequence (32) may also contribute to the diversity of peptides with potential for competition with 9pp89. A third source of competing ENV-related peptides could be the extracellular space or the cell membrane (33). Thus, the efficient processing of ENV at several relevant subcellular sites may make it a good source of competing peptides of sufficient affinity for Ld. Differences in the epitope itself, as shown in this study for strain MN, or in these other properties, might contribute to the differential pathogenicity of HIV strains.

The experiments with Ld mutants showed different relative competition strength of the two ENV-expressing competing constructs in transfectants that possess identical endogenous processing pathway, and only differ in point-mutated MHC class I molecules. In addition, quantitation of naturally processed 9pp89 peptide in cells expressing the competitor showed lower amounts of antigenic peptide. Also, the amount of processed peptide that was produced under different experimental conditions correlated inversely with the susceptibility to competition by ENV. This set of data therefore suggests that competition is not due to preferential cleavage by the proteasome or to differential transport by TAP of any 9pp89-related precursor peptide (34). Rather, we place the step of competition at a level where MHC class I molecules are involved, particularly at the stage of MHC/peptide complex assembly and stability. Interference would thus be explained by competition between different peptides for binding to Ld. Complex formation occurs in the ER (35), which is where competition may primarily occur. Peptide exchange at a later step in the secretory pathway (36), associated with further points of ENV peptide generation as discussed above, may contribute as well.

Competition should occur under conditions of limited resources. For example, only strongly binding peptides should complex with limited MHC class I molecules, whereas under excess amounts of MHC, weaker peptides would also have the chance to bind. It has been estimated that TAP translocates 20,000 peptides every minute per cell into the ER, whereas only ~100 peptide-receptive MHC class I molecules are synthesized during this time (37). In such a situation of MHC shortage, it is feasible that a potentially higher production in a relevant site of efficiently binding ENV peptides would lead to a disadvantage for CMV epitope binding.
Deficient endogenous presentation of an Ag may arise from inefficiencies in any of the sequential processes of degradation, TAP-dependent transport, and MHC class I binding. In this study we showed that the presentation of an immunodominant epitope is also conditioned by the presence of another dominant epitope. Two studies on CTL responses to HIV (2) and lymphocytic choriomeningitis virus (1), showing that weak epitopes are suppressed in the presence of stronger epitopes, although these weak epitopes are able to generate a competent response if expressed in isolation, could be interpreted accordingly. Also, the reverse situation of what is reported in this study has been described; namely, competition between MHC class I alleles for presentation of overlapping viral epitopes that resulted in suboptimal loading of one of the alleles in vitro (38). Altogether, competition for the same MHC class I molecule appears to represent a mechanism that can modulate presentation, whereas it may not operate for MHC class II (39).

These data highlight potential limitations in the design of recombinant vaccines expressing mixtures of immunodominant epitopes from HIV ENV and other pathogens. In multiepitope vaccine studies not involving ENV, observations compatible with partial interference have not been studied further (40, 41). When the ENV epitope was included, a substantial role of the relative location of two epitopes in the efficiency of class I presentation both in vitro and in vivo was seen (41). Whether or not Ag competition by ENV or other Ags is a frequent event cannot be decided yet, although different HIV ENV strains already differ in these properties. It is also not clear whether this would apply to all MHC molecules, because the results reported in this study also stress the importance of MHC sequence differences for the outcome of competition. From what is known about immunodominance of epitopes within a single pathogen (2, 3, 42), Ag competition might not be a rare event. The real situation may lie somewhere between strong competition and complete liberty of presentation. Previously, only intrinsic features of the epitope (MHC affinity and peptide libera- tion) and its necessary partners (T cell repertoire and APC) have been implicated as influencing immunodominance. Now we describe in detail the mechanism that underlies the further qualitative level that contributes to immunodominance, which is the presence and properties of fellow epitopes. Thus, we show a way in which circumstances external to the epitope itself can preclude its presentation.

Moreover, coinfection of the same cells by HIV and CMV also occurs in vitro (43) as well as naturally, Interestingly involving APC, particularly in the CNS (44, 45). In patients with AIDS, CMV causes severe retinitis, is associated with neurological damage, and represents a recurrent primary pulmonary pathogen (46).

References


