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Sequence Homology and Immunologic Cross-Reactivity of Human Cytomegalovirus with HLA-DR β Chain: a Means for Graft Rejection and Immunosuppression†

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A peptide (Leu-Gly-Arg-Pro-Asp-Glu-Asp-Ser-Ser-Ser-Ser-Ser-Ser-Ser-Ser-Cys) that was identical to residues 82 through 96 of a predicted protein of 208 amino acids from the immediate-early region (IE-2) nucleic acid sequence of human cytomegalovirus was chemically synthesized. By computer analysis, the first five amino acids of this peptide showed sequence homology to the β chain of the human histocompatibility complex HLA-DR. The homologous amino acids, 53 through 57, were located in a region that is conserved between the human DR β chain and the β chain of the H-2 class II histocompatibility antigen for mice. The shared region between the IE-2 protein and DR β chain were similar in both hydrophilicity and predicted β-turn potential. The IE-2 viral peptide induced antibodies that specifically recognized the human DR β chain. These observations describe a protein encoded by the IE-2 region of human cytomegalovirus that contains sequence homology and shows immunologic cross-reactivity with a conserved domain of HLA-DR and suggest a mechanism to explain how human cytomegalovirus infection contributes to graft rejection after transplantation.

Human cytomegalovirus (HCMV) infection is associated with foreign graft rejection (10, 15, 16). For example, acute HCMV infection occurs in the vast majority of patients after organ transplantation (5, 10), and frequently the severity of infection parallels the incidence of graft rejection. Additionally, the incidence of HCMV shedding by women rises from 1 to over 13% during pregnancy (2). HCMV has been hypothesized to play an important role in whether the graft survives (5, 10). This may be due to a direct effect of the virus on the target tissue causing irreversible damage or the immune system responding to viral sequences present in transplanted cells.

Transplantation antigens are encoded by genes in the major histocompatibility complex (HLA in humans, H-2 in mice). HLA-DR antigens are glycoproteins found predominantly on the surface of B cells and certain macrophages. DR antigens are comprised of two chains in a noncovalent association. An entire cDNA clone of the DR β chain has been sequenced, and the predicted amino acid sequence has been established (32). The amino-terminal domain shows homologous regions with HLA-A, -B, and -C heavy chains (12). Molecules corresponding to DR in the mouse (Ia) can stimulate a mixed leukocyte reaction, production of potent antibodies, a graft-versus-host reaction, and, in some instances, graft rejection. Further, most antigens must be presented to T cells in the context of these class II molecules for an immune response to be mounted (reviewed in reference 22).

HCMV is a member of the herpesvirus group, and its transcription can be divided into three separate phases: immediate early (IE), early (E), and late (L) (7, 30). Recent evidence indicates that during viral latency transcription is restricted to IE (21, 23) and perhaps E products and suggests that IE products are recognized by HCMV-specific cytotoxic T lymphocytes (4, 18–20). The IE genes are transcribed in the absence of viral protein synthesis and are located in restriction areas 0.709 to 0.741 of the genome (11, 30).

For the experiments reported here, we focused on IE genes of HCMV and HLA determinants. We asked three questions. First, do any of the encoded IE proteins contain amino acid sequences that are also shared by HLA proteins? Second, are the homologies significant? Third, can cross-reacting immunologic reagents be generated that bind to both viral and HLA (self) proteins?

Here we report our results that the IE-2 protein of HCMV and the HLA β chain share a common epitope. Further, antibody produced against the HCMV peptide binds to the β chain of HLA-DR antigen. These findings indicate a mechanism to explain how a virus infection can be associated with transplant rejection.

MATERIALS AND METHODS

Analysis of proteins, synthesis of selected peptides, and generation of antibodies to predetermined amino acid sequences. IE and HLA proteins were compared for homologous amino acid sequences by using the protein sequence data base (6). Areas of interest were studied for both hydrophobicity and β-turn potential (6). Peptides were synthesized by solid-phase methods developed by Merrifield (14) with an automated Applied Biosystem 430A. For immunization, peptides were coupled to keyhole limpet hemocyanin (KLH) by using *m*-maleimidobenzoyl-*N*-hydroxysuccinimide ester (MBS) as an intermediate (13). Briefly, 85 μl of MBS at 6 mg/ml in dimethylformamide was mixed with 4 mg of KLH in 55 μl of 10 mM phosphate buffer (pH 7.2). The mixture was incubated at room temperature for 30 min and then applied to a Sephadex G-25 column equilibrated with 50 mM phosphate buffer (pH 6.0). The protein peak (KLH-MBS) was pooled. Then, 5 mg of peptide in 100 mM

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phosphate buffer (pH 7.2) was added to 3.2 mg of KLH-MBS, and the pH was adjusted to 7.2. The mixture was stirred for 3 h at room temperature and inoculated into rabbits or aliquoted and stored at −20°C. The immunization schedule of rabbits consisted of a primary subcutaneous injection of 200 μg of peptide-KLH in complete Freund adjuvant (2 mg of mycobacterium per ml). Two weeks later a secondary immunization consisting of 200 μg of peptide-KLH in incomplete Freund adjuvant was administered subcutaneously. Three weeks later the rabbits were boosted with 200 μg of peptide-KLH in alum intraperitoneally, and serum samples were obtained 7 and 14 days after the third injection.

Immunochemical analysis. A microtiter 96-well plate was coated with 0.5 μg of free peptide per well and assayed at room temperature. Unbound reactive sites were blocked by incubation for 1 h with 0.2% Tween 20–10% fetal bovine serum–0.5 mM Thimerosal in phosphate-buffered saline (enzyme-linked immunosorbent assay buffer). The plates were incubated for 1 to 2 h with various rabbit sera diluted in the same buffer, and unbound material was removed by washing (five times) with 0.2% Tween 20 in phosphate-buffered saline. Peroxidase-labeled, affinity-purified goat anti-rabbit immunoglobulin G was added for 2.5 h, plates were washed five times, and substrate (0.4 mg of *O*-phenylenediamine per ml–0.1% H_2O_2 in citrate buffer, pH 5.0) was added for 30 min. Negative controls included preimmune or normal rabbit sera and incubations without first or second antibodies.

Lymphoblastoid cells (LG-2 and GM-3107) were coated to microtiter plates as described by Varki et al. (28). An enriched HLA-DR glycoprotein preparation was isolated from the cell line LG-2 by affinity chromotography on *Lens culinaris* lectin-Sepharose (3).

For electrophoretic transfer blotting analysis, glycoproteins (5 μg per lane) were mixed with 100 μl of 0.068 M Tris hydrochloride (pH 6.8) containing 2% sodium dodecyl sulfate and 5% (vol/vol) 2-mercaptoethanol and heated for 2 min at 100°C. The antigen preparation was separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (12.5% acrylamide) and electrophoretically transferred to a nitrocellulose sheet as described by Towbin et al. (26). To reduce nonspecific binding of the antiserum, the nitrocellulose sheets were first incubated for 2 h with 0.01 M Tris hydrochloride buffer (pH 7.4) containing 0.5 M NaCl and 3% (wt/vol) bovine serum albumin. The blots were then incubated at room temperature for 2 h with either 10 ml of rabbit antiserum diluted in phosphate-buffered saline containing 0.2% bovine serum albumin and 0.2% Tween 20 or with 10 ml of monoclonal antibody (5 μg/ml) in the same buffer. After five washes in phosphate-buffered saline containing 0.2% Tween 20 and 0.1% ovalbumin, the blots were incubated for 1 h with 10 ml of a 1:100 dilution of staphylococcal protein A conjugated to horseradish peroxidase (Sigma Chemical Co.). After an additional five washes with the same buffer, the binding of antibodies was visualized by incubation at room temperature with 10 ml of 0.01 M Tris hydrochloride (pH 7.4) containing 0.8 mM *o*-dianisidine dihydrochloride and 0.001% H_2O_2. The reaction was stopped by washing with water containing 0.02% sodium azide.

RESULTS

IE protein homology with HLA-DR. At least five IE genes have recently been uncovered (25). The major 1.9-kilobase mRNA encodes a 72-kilodalton (kDa) protein (11). A region 3′ to the major IE gene encodes a series of at least four mRNAs ranging in size from 1.1 to 2.5 kilobases. These encode for predicted proteins ranging in size from 16,500 to 56,000 kDa (24) and are termed IE-2. One region from IE-2 predicted proteins showed homology with HLA-DR. Hence, over 530,000 comparisons were made of the hydrophilic region (Leu-Gly-Arg-Pro-Asp-Glu-Asp-Ser-Ser-Ser), amino acids 82 to 91, of the HCMV IE-2 protein with other proteins in the Dayhoff data base; the first five amino acids (Leu-Gly-Arg-Pro-Asp) were found to be identical with those of the HLA-DR β chain (amino acids 53 through 57) (Fig. 1). With the Kyte-Doolittle hydrophobicity analysis, homologous regions of HLA-DR and IE-2 peptides showed a high degree of hydrophilicity and predicted β-turn potentials (Fig. 1). These data suggest that the homologous shared regions of IE-2 sequence 82 to 91 and of HLA-DR sequence 53 to 57 would be found on outer regions of the parent molecules.

Immunologic cross-reactivity between IE-2 and HLA-DR molecules. A viral peptide, Leu-Gly-Arg-Pro-Asp-Glu-Asp-Ser-Ser-Ser-Ser-Ser-Ser-Ser-Cys, containing the common site at its amino terminus was synthesized, and its purity of 80% was established by high-pressure liquid chromatographic analysis. The sequence was obtained from Stenberg et al. (25). The peptide was coupled to KLH via the carboxyterminal Cys and inoculated into rabbits to generate antibodies to predetermined amino acid sequences. Figure 2A demonstrates the specific reactivity of these antibodies to native HCMV protein expressed in infected fibroblasts and to the immunizing viral peptide. The titer to the IE-2 peptide was greater than 1:40,960 and that to HCMV-infected cells was greater than 1:10,240. Little or no reactivity was observed with mock-infected fibroblasts, irrelevant peptides, or uncoated wells. The reactivity of this antipeptide antiserum as well as the reactivities of additional antipeptide antibodies to the IE-2 region of HCMV has been described by Stinski and colleagues (9a).

A second series of experiments showed that antibody to IE-2 peptide sequence 82 to 91 bound to HLA-DR antigens. In these experiments, two different B-lymphocyte lines, LG-2 and GM-3107, were attached to plastic wells and assayed. As determined by enzyme-linked immunosorbent assay, the anti-IE-2 HCMV peptide sera specifically bound to both cell lines. LG-2 cells quantitatively had more accessible DR antigen than GM-3107 cells (Fig. 2B). Using this data we then studied the ability of the antibody to HCMV IE-2 peptide to bind to HLA-DR glycoprotein isolated from LG-2 cells by lectin affinity chromatography and analysis of Western blots (immunoblots). The antibody to viral peptide reacted with the HLA-DR β chain (29 kDa) (Fig. 3). Immunologic specificity was shown since the binding could be inhibited by addition of viral peptide (Fig. 3).

DISCUSSION

Here we provide evidence that a region from the HCMV IE-2 codes for an amino acid sequence also present on the HLA-DR β chain. The common area from both sequences is hydrophilic and has predicted β-turn potential, suggesting that the epitope is located on the external surface of the protein. Others have shown that five amino acids are sufficient to fit into the binding pocket of an antibody molecule (31), suggesting that our common five-amino-acid sequence shared by two dissimilar proteins, HCMV IE-2 and HLA-DR, might be recognized by an antibody response generated against one of them.

The viral IE-2 and the HLA-DR sequences were antigenically identical. Antibody to the IE-2 product reacted with

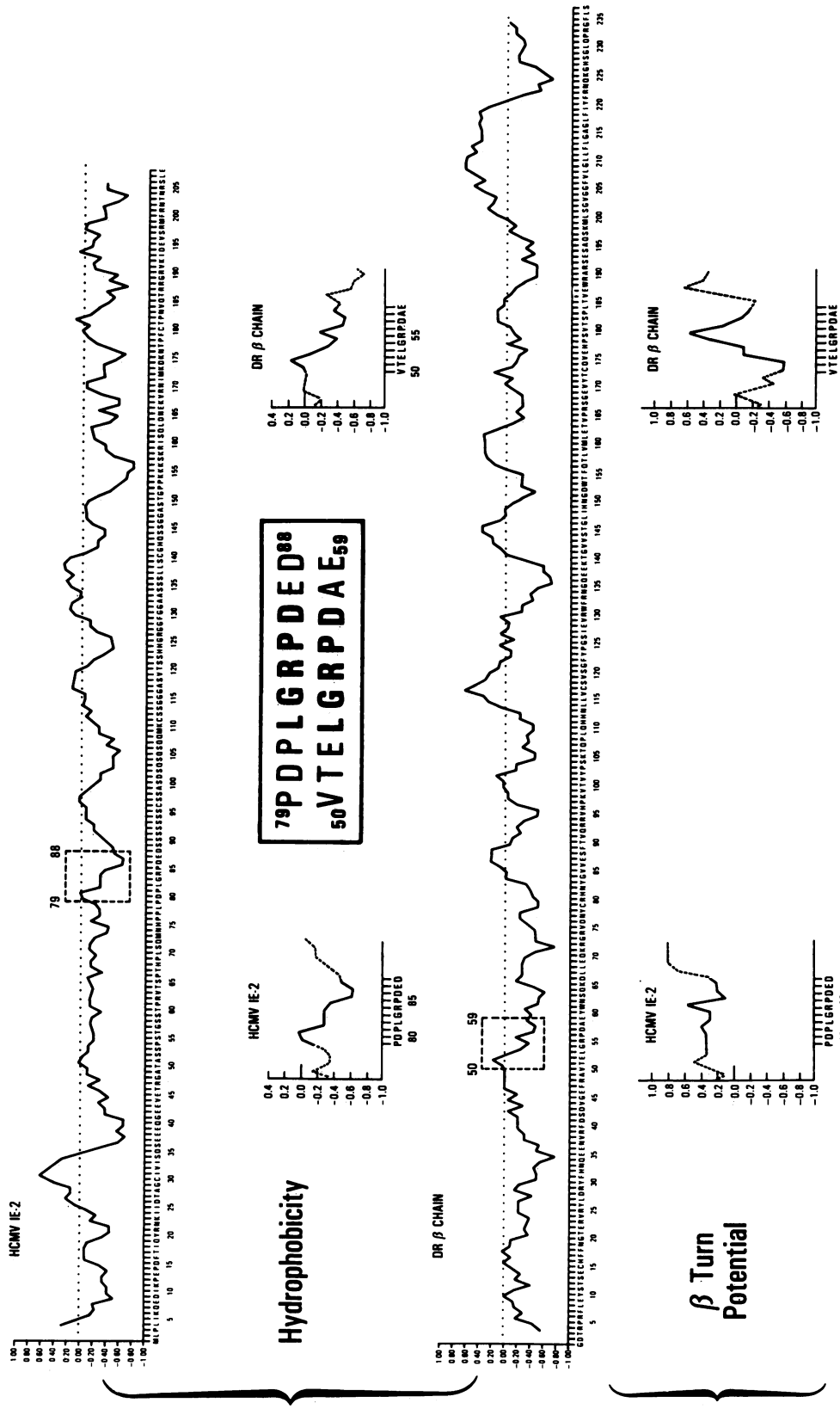

FIG. 1. Hydrophobicity plot of IE-2 protein and HLA-DR β chain. Common regions between the two dissimilar proteins are boxed in the center. The β-turn potential of IE-2 protein and HLA-DR β chain of the common regions is also shown.

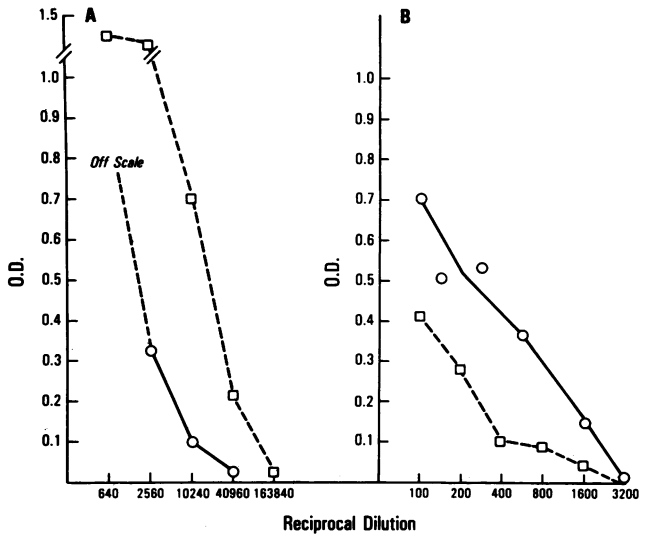

FIG. 2. (A) Enzyme-linked immunosorbent assay reaction showing the antibody against IE-2 predetermined amino acid sequences (Leu-Gly-Arg-Pro-Asp-Glu-Asp-Ser-Ser-Ser-Ser-Ser-Ser-Ser-Cys) bound to both HCMV infected fibroblasts (○) and the IE-2 peptide (□). Binding to uninfected fibroblasts has been subtracted from values for HCMV-infected fibroblasts. (B) Enzyme-linked immunosorbent assay reaction of antibody against IE-2 predetermined amino acid sequences (Leu-Gly-Arg-Pro-Asp-Glu-Asp-Ser-Ser-Ser-Ser-Ser-Ser-Ser-Ser-Cys) bound to cell lines that preferentially express HLA-DR antigens and are not infected with HCMV. Lymphoblastoid lines LG-2 (○) and GM-3107 (□) are shown. Binding of normal rabbit serum has been subtracted out. O.D., Optical density.

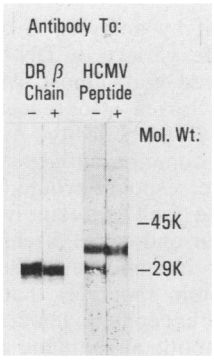

FIG. 3. Western blot analysis of binding of antibody against IE-2 predetermined amino acid sequences (Leu-Gly-Arg-Pro-Asp-Glu-Asp-Ser-Ser-Ser-Ser-Ser-Ser-Ser-Cys) to HLA-DR antigen. HLA-DR antigens extracted from LG-2 uninfected cells and enriched by lectin affinity chromotography were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The right two lanes demonstrate reaction of antibody to predetermined IE-2 amino acid sequences to HLA-DR 29-kDa antigen (−) and the inhibition of IE-2 peptide antibody binding by addition of HCMV peptide (+). The left two lanes are controls that show the binding of a monoclonal antibody to HLA-DR β chain to the HLA-DR 29-kDa antigen (−) and the inability to inhibit binding of HLA-DR with HCMV peptide (+). The monoclonal antibody to HLA-DR β chains is directed to a different epitope than the antibody to IE amino acid sequences.

HCMV-infected cells as well as on HLA-DR antigen-positive cells that were not infected with HCMV. Further, the antibody reacted with the 29-kDa HLA-DR β chain (Fig. 3), and its binding was specifically inhibited with IE-2 free peptide. Since the binding of the antipeptide antibody to the 29-kDa HLA-DR β chain was inhibited by free peptide, the common epitope was involving in the binding.

These experimental findings suggest a scenario of how HCMV could participate in rejection of a foreign graft. Immunologic attack against HLA molecules leads to allo-reactions and tissue rejection, whereas the IE region codes for proteins that are made during latency, are actively transcribed during acute infection and are recognized by both cellular (virus-specific H2 restricted cytotoxic T lymphocytes) and humoral (antibody) immune responses (4, 18–21, 23). The transcription and splicing of RNA and predicted proteins from the IE-2 region have been described previously (25). Rice et al. (21) and Schrier et al. (23) have demonstrated the expression of IE-1 products in latent HCMV infections. Our data indicate that HLA-DR and HCMV IE-2 sequences are sufficiently similar that an immune response generated against the virus is also able to react with "self" HLA-DR. Further, the HLA-DR antigen is an integral membrane molecule that is accessible to react against antibodies or (Fig. 2 and 3) cytotoxic T lymphocytes, and the sequence homology observed between its β chain and HCMV IE-2 is from a conserved region of the β chain. Thus, an immune response generated against HCMV IE-2 sequences could also react against DR "self" antigens. Presumably, the more severe the disease, i.e., HCMV replication, the greater the response against DR. Additionally, the enhanced microcirculation accompanying the transplanted site likely attracts lymphoid cells that are transported to and accumulate at the area of local inflammation (reviewed in references 17 and 26). In support of this idea, we recently detected an enrichment of inflammatory cells containing HCMV IE transcripts in transplanted kidneys undergoing graft rejection as compared with those in peripheral blood (J. Gnann, L. Olding, M. B. A. Oldstone, and J. Nelson, unpublished data and submitted for publication). In addition, van Es et al. (27) have described the expression of HLA-DR on human T lymphocytes after renal transplantation. In patients who suffered rejection events an increase in DR expression was found. The increase in HLA DR expression coincided with the onset of clinical symptoms of HCMV infection. The level of DR antigen returned to normal after symptoms of infection disappeared. More recently, von Willebrand et al. (29) demonstrated that during renal graft rejection, class II antigen expression is increased in parenchymal cells of the graft. HCMV infection was associated with the upregulation of the class II antigen. These investigators (27, 29) suggested that the increased expression may be due to gamma interferon production during infection. Our data suggest that an alternative explanation would be the presence of the cross-reacting epitope.

Other ways that HCMV could induce graft rejection would be immunologic recognition of expressed viral IE products in infected kidney cells. This type of recognition would most likely involve recognition of viral peptide sequences in the context of major histocompatibility complex class I. HCMV could also induce the production of autoantibodies through polyclonal B-cell activation. Other members of the herpesvirus group have been reported to have this property (reviewed in reference 1). Epstein-Barr virus is the best characterized. In this process, transformation and polyclonal activation of human B cells are closely associated. Individuals with Epstein-Barr virus mononucleosis have autoantibodies in their circulation.

The sharing of a microbial epitope with a host "self" epitope from two dissimilar proteins has been termed molecular mimicry (8, 9). Molecular mimicry is a common

occurence as judged by analysis of over 600 monoclonal antibodies to a wide variety of DNA and RNA viruses. Those studies showed that almost 4% of the monoclonal antibodies against viruses also reacted with host "self" determinants (24). Hypothetically, during infection by a virus that shared a common antigenic epitope with a host protein, the immune response would be generated against both the virus and the "self" protein. Evidence that this type of reaction can occur and cause disease was recently demonstrated when an immune response generated in vivo against a viral protein (peptide) that shared amino acid sequences with the encephalitogenic site on myelin basic protein resulted in both an immune response against the native myelin protein and tissue injury characteristic of allergic encephalomyelitis (9). These data and the results reported here suggest that a similar pathogenetic mechanism may explain postinfectious encephalomyelitis and peripheral neuropathies (Gullian-Barre syndrome), dementias, demyelination, and hemorrhagic and coagulation defects after viral infections. Experiments to clarify these contentions are underway.

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