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Epitope Mapping of the Major Epstein–Barr Virus Outer Envelope Glycoprotein gp350/220

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SUMMARY

To understand the complete immunochemical structure of the Epstein–Barr virus (EBV) major membrane glycoprotein gp350/220, monoclonal antibodies (MAbs) reacting with this important viral antigen were isolated. Through competitive inhibition binding studies, it was determined that a group of 18 IgG MAbs recognized seven distinct epitopes on the gp350/220 molecule. Eight of these MAbs fell into a single epitope group with four of those MAbs, as well as a single MAb from another epitope group, being capable of neutralizing EBV strain B95-8 transformation of umbilical cord lymphocytes.

INTRODUCTION

Infection by Epstein–Barr virus (EBV) is ubiquitous, reaching 70 to 100% of individuals in all societies (Black *et al.*, 1970; Lange *et al.*, 1977). To date, EBV has been established as the aetiological agent of infectious mononucleosis (Henle & Henle, 1979) and is implicated in a polyclonal lymphoma in immunodeficient people (Purtilo *et al.*, 1981). Substantial evidence also links EBV with two types of human cancer: Burkitt's lymphoma and nasopharyngeal carcinoma (de The, 1982). Thus, prevention or limitation of EBV infection with an effective vaccine should be of substantial benefit to people at risk of infection with EBV.

The oncogenic potential of EBV mandates that any potential vaccine be completely free of any transforming activity. One approach to developing a vaccine under this constraint would be to identify first the antigens on the virus responsible for inducing immunity during infection and then to dissect immunochemically those antigens to determine the relevant epitopes responsible for eliciting that immunity. An *in vitro* synthesized subunit vaccine can then be constructed containing these epitopes and used to elicit a protective antibody response. A principal membrane glycoprotein gp350/220, found on EBV, is a likely antigen to be considered in any EBV vaccine. Work in several laboratories has shown that both polyclonal and monoclonal antibodies directed against gp350/220 are capable of neutralizing viral infectivity (Beisel *et al.*, 1985; Thorley-Lawson & Geilinger, 1980; Thorley-Lawson & Poodry, 1982) and mediating antibody-dependent lymphocyte cytotoxicity (Qualtiere *et al.*, 1982*a*, *b*). Furthermore, it has been shown that much of the neutralizing activity contained in EBV-seropositive human serum is directed against this protein (Thorley-Lawson & Poodry, 1982). Work presented in this study utilizing 18 monoclonal antibodies (MAbs) reports the finding of seven distinct epitopes on the EBV gp350/220 molecule. Two of these epitopes are shown to be capable of eliciting neutralizing antibody capable of preventing EBV infection of umbilical cord blood lymphocytes.

METHODS

Cell lines. The cell lines used in this study included the standard P_3HR-1 virus-producing cell lines, and the 1605L cell line, a high membrane antigen-expressing clonal isolate of B95-8, received from H. Rabin (Qualtiere & Pearson, 1980). In addition to these producer cell lines, the human Burkitt lymphoma lines Raji and Ramos were used. All human cell lines were grown in RPMI 1640 medium containing 5% heat-inactivated foetal bovine serum

(FBS), plus 0·0173 mg/l sodium selenite and 25 μg/ml gentamicin. Mouse myeloma lines P_3NS-11-AG4-1 and FO were used for MAb production. These cells were grown in the same medium as the human lines, except that it was supplemented with 2 mM-sodium pyruvate.

Immunization. Mice were immunized with 1×10^7 1605L cells, activated 3 days earlier with 40 ng/ml phorbol 12-myristate 13-acetate (TPA). Such cultures generally contained 30 to 40% membrane antigen (MA)-positive cells. For immunization, viable cells were emulsified with an equal volume of complete Freund's adjuvant and injected intraperitoneally. In some cases, spleens for the production of hybridomas were removed 4 days after the initial immunization, but for the majority of the hybridoma productions the spleens were removed 1 to 7 months after the initial immunization during which time the animals were boosted an additional one to three times intraperitoneally with 1×10^6 TPA-activated 1605L cells emulsified in incomplete Freund's adjuvant. Hybridomas were established according to the protocol previously described in detail (Qualtiere *et al.*, 1982*b*). After 10 to 14 days, wells with visible clones were assayed for antibodies to EBV-induced MA by an indirect immunofluorescence assay. The supernatant fluid was first tested against an EBV MA (positive) line (1605L or P_3HR-1) and if positive, then against a negative MA line such as Raji or Ramos. The wells containing antibody-positive clones for EBV MA were expanded into 24-well culture plates and then subsequently cloned by two cycles of limiting dilution cloning. The cloned positive hybridomas were then injected into mice primed 10 to 14 days previously with 0·3 ml pristane for the production of antibody-containing ascites fluid.

Membrane immunofluorescence (MF assay). Original hybrid clones were selected and then characterized utilizing an indirect MF assay for EBV-induced MA utilizing fluorescent conjugated goat or rabbit anti-IgG (Cooperbiomedical, Malvern, Pa., U.S.A.) according to previously described procedures (Qualtiere *et al.*, 1982*a*, *b*). Modification of the indirect MF assay was used to determine subclass specificity. In this analysis, TPA-activated 1605L cells (5×10^6) were first incubated with 200 μl tissue culture fluid containing MA-positive MAb for 30 min at 37 °C and then washed twice with 0·01 M-phosphate-buffered saline, 0·1 M-NaCl pH 7·2 (PBS) containing 3% newborn calf serum (NCS). Cells were then split into five separate aliquots and to each individual aliquot was added 15 μl of a 1:800 dilution of subclass-specific rabbit anti-mouse IgG1, IgG2a, IgG2b, IgG3 or IgM (Cooperbiomedical). Following another 30 min incubation at 37 °C and two washings in PBS, 3% NCS, a goat anti-rabbit fluorescent conjugate was added. Following a final incubation for 30 min at 37 °C and two additional washes, the cells were mounted and viewed through a Reichert Jons Polyvar fluorescence microscope.

Immunoprecipitation. MA-positive cells, surface-labelled by the lactoperoxidase method with ^{125}I as described by Qualtiere & Pearson (1979), were mixed with 1% NP40 in PBS containing 2 mM-phenylmethylsulphonyl fluoride (Pearce, Rockville, Ill., U.S.A.) at a concentration of 1 ml solvent per 2×10^7 cells. After 30 min at 25 °C, nuclei and particulate matter were removed by centrifugation of the NP40-solubilized cells at 10000 ***g*** for 1 h. The supernatant fluid was then decanted and exhaustively dialysed against 0·1% NP40–PBS for 2 days. For radioimmunoprecipitation, aliquots of the extract containing 1×10^6 to 5×10^6 c.p.m. of ^{125}I were added to 50 μl antibody-negative or antibody-positive ascites in the presence of PBS supplemented with 1% bovine serum albumin and 0·1% NP40. Mixtures were then incubated overnight at 4 °C. Immune complexes were removed by immunoprecipitation with Protein A–Sepharose 4B (Pharmacia) as detailed elsewhere (Qualtiere & Pearson, 1980), or with Sepharose 4B coupled directly to rabbit anti-mouse IgG (Cooperbiomedical). The washed immune complexes were then analysed for the presence of EBV-specific membrane components utilizing the SDS–polyacrylamide gel electrophoretic system of Laemmli (1970), as previously described (Qualtiere & Pearson, 1979).

Immunoglobulin isolation and labelling. Purified IgG fractions from the MAbs utilized in this study were obtained by DEAE ion-exchange chromatography of ammonium sulphate precipitates of ascites fluid as described in detail previously (Staehelin *et al.*, 1981). For use in the competitive binding assay, all DEAE-purified IgG fractions were labelled with ^{125}I by the chloramine T method (Greenwood *et al.*, 1963). Chloramine T was added (5 μg in 10 μl 0·1 M-sodium phosphate buffer pH 7·5) to a tube containing 100 μl of the sodium phosphate buffer pH 7·5 containing 50 to 100 μg purified IgG and 500 μCi sodium ^{125}I (450 μCi/ml, New England Nuclear). The reaction was terminated after 60 s by the addition of 50 μg sodium metabisulphite in 50 μl sodium phosphate buffer. Free ^{125}I was removed by gel filtration through a 5 ml G-25 Sephadex column. The ^{125}I-labelled immunoglobulins ranged in specific activity from 0·2 to 0·05 μCi/μg. When the binding activity of the various MAbs was measured after labelling, it was found that 5 to 80% of the original binding activity had been retained. Preliminary titrations on TPA-activated 1605L cells found that those immunoglobulins whose binding activity fell below 25% of the total immunoglobulin labelled were unsuitable for competitive binding assays. Four immunoglobulins fell into this category. These were F30-5C8, F34-1D8, F34-6B1 and 2F5.6. To tag these immunoglobulins, an alternative labelling procedure was selected that utilized terminal amino acid groups rather than tyrosine residues for introduction of the label. Instead of ^{125}I labelling, fluorescein isothiocyanate (FITC) was directly coupled to these MAbs by a standard procedure (The & Feltkamp, 1970). All four MAbs retained significant (>75%) binding activity after coupling with FITC.

Competitive binding assay. To evaluate the ability of the 18 IgG MAbs to inhibit specifically the binding of one another, 1×10^6 TPA-activated 1605L cells in 0·1 ml PBS were mixed first with 0·1 ml of various concentrations

of DEAE-purified MAb ranging from 1 mg/ml to 0·01 mg/ml. The antibody:cell mixture was incubated for 15 min at room temperature and 1 to 2 μg ^{125}I-labelled MAb was then added to each tube. The reactants were mixed and incubated for an additional 30 min at room temperature. After cells were washed three times with 1 ml PBS, 3% NCS, the final cell pellet was drained and counted in a Beckman 7000 Gamma Spectrophotometer.

Cord blood neutralization. Umbilical cord blood was obtained from the Obstetrics and Gynecology Department, University Hospital, Saskatoon. Leukocytes from the cord blood were isolated by a standard Ficoll–Hypaque procedure (Boyum, 1968). Leukocytes were counted and adjusted to 1 × 10^6 cells/ml in RPMI 1640 medium, 20% FBS and 40 μg/ml gentamicin, and dispensed into 24-well plates, 1 ml/well. Initial neutralization tests for each of the MAbs were performed with a 1:10 dilution of ascites fluid. To tubes containing 100 ID_{50} of B95-8 virus in 0·1 ml medium was added 0·1 ml of a 1:10 dilution of each of the MAb-containing ascites. The antibody–virus mixture was incubated at 37 °C for 1 h and plated, or 0·1 ml of a 1:5 dilution of guinea-pig complement was added to the mixture and the incubation continued for an additional hour at 37 °C. The contents of the tubes were then added to the 1 ml of umbilical cord cells present in the 24-well plates. The plates were then incubated at 37 °C in 5% CO_2 atmosphere, the media were changed weekly, and the cells were examined at regular intervals over a 1 month period. The neutralization was scored 25 to 35 days after inoculation by the inhibition of outgrowth of transformed cells in at least three of the four quadruplicate wells. Those MAbs showing significant neutralization at a 1:10 dilution were further tested at a 1:100 and 1:1000 dilution of ascites fluid.

RESULTS

Monoclonal antibody production

To generate a large number of MAbs to gp350/220, mice were immunized with 40% MA-positive, TPA-activated 1605L cells using both short-term and long-term immunization protocols. From a total of 23 fusions, over 3500 clones were screened against a battery of EBV-producer and non-producer cells and only those showing the very strong full ring fluorescence characteristic of previously described gp350/220 MAbs (Qualtiere *et al.*, 1982*b*) were saved. A total of 18 IgG and four IgM EBV MA-specific MAbs were finally selected. Thirteen of the MAbs were of the IgG1 subclass, but representatives of all but the IgG3 subclass were present (Table 1). Although all the MAbs displayed strong EBV MA-specific staining on EBV-producer cell lines, not all were capable of precipitating an EBV-specific antigen from ^{125}I-labelled, NP40-solubilized MA-positive cells. These included two members of the IgM and three members of the IgG1 subclass (see lane 3, Fig. 1). Other MAbs like F30-5C8 precipitated gp350/220 only weakly (see lane 8, Fig. 1). Most, however, as shown in lanes 1, 2, 4, 5, 6, 7 and 9 of Fig. 1 and in Table 1, precipitated the ^{125}I-labelled gp350/220 molecule very well. The reason for the differential ability of the various MA-specific MAbs to precipitate labelled antigen from the ^{125}I-labelled NP40 extract is unknown, but may be due to antibody affinity and/or conformational changes occurring to the gp350/220 molecule during detergent solubilization.

Epitope mapping

Having determined by radioimmunoprecipitation (Table 1, Fig. 1) that we had at least 15 IgG MAbs specific for the gp350/220 molecule, we carried out competitive binding experiments to determine the number of different epitopes recognized by these MAbs. For these competitive binding experiments, all the IgM MAbs were not included to avoid possible confusion due to the large IgM molecule sterically blocking more than one epitope on the gp350/220 molecule. Those IgG MAbs which had displayed the immunofluorescent staining, characteristic of the anti-gp350/220 MAbs, but which were unable to precipitate the molecule, were initially included in the competitive binding assays. Clearly, the ability of any of these non-precipitating MAbs to block specifically other MAbs previously demonstrating certain gp350/220 specificity would be sufficient reason to allow their inclusion in the study.

The determination of the number of different epitopes recognized by this battery of gp350/220-specific MAbs is based on the ability of those MAbs recognizing the same epitope to block reciprocally the binding of one another to the surface of MA-positive cells. To measure this competitive binding, 1605L cells, > 30% MA-positive were incubated first with a high concentration of each of the unlabelled MAbs, followed 30 min later by the addition either of ^{125}I or FITC-tagged MAb. Ability of each of the untagged MAbs to block the binding of the labelled MAbs over the range of inhibitory antibody concentrations used was then measured. An

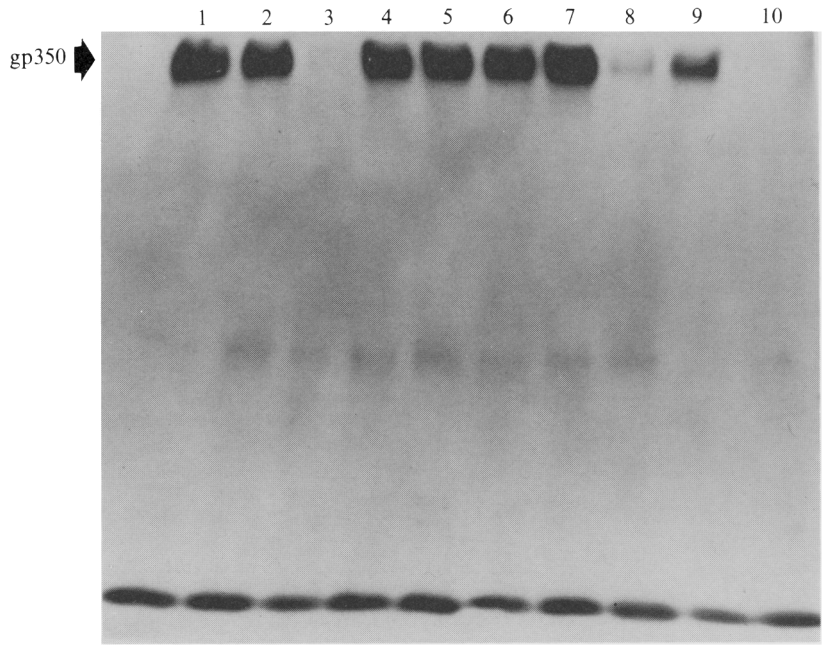

Fig. 1. Autoradiograph of a 7·5% SDS gel profile analysing the ^{125}I-labelled proteins precipitated by several EBV-specific MAbs. Lane 1, F16-3E3; lane 2, F29-89; lane 3, F30-3C6; lane 4, F16-11B7; lane 5, F16-1C10; lane 6, F34-5H7; lane 7, F37-2B11; lane 8, F30-5C8; lane 9, F34-1D8; lane 10, negative ascites.

Table 1. *Immunochemical characterization of EBV-specific MAbs*

EBV membrane antigen-specific MAb*	Subclass	gp350/220 specificity
2F5.6	IgG2b	+†
B10.3	IgM	−‡
F16-3E3	IgG1	+
F16-11B7	IgG1	+
F16-1C10	IgG1	+
F29-167	IgG2a	+
F29-89	IgG1	+
F29-24	IgM	−
F30-3C6	IgG1	−
F30-3C2	IgG1	+
F30-3F12	IgM	+
F30-2G8	IgM	+
F30-5C8	IgG2a	+
F34-5D3	IgG1	+
F34-1D8	IgG2b	+
F34-1F2	IgG1	+
F34-4E3	IgG1	−
F34-2B11	IgG1	+
F34-6B5	IgG1	−
F34-5H7	IgG2a	+
F34-6B1	IgG1	+
F34-4G8	IgG1	+

* Determined by indirect immunofluorescence by testing their reactivities on a series of virus-producing and non-producing cell lines (see Methods for details).

† Ability of MAbs to immunoprecipitate gp350/220 from ^{125}I-labelled NP40-solubilized B95-8 cells.

‡ Inability to determine the molecular weight of the antigen recognized by the MAb.

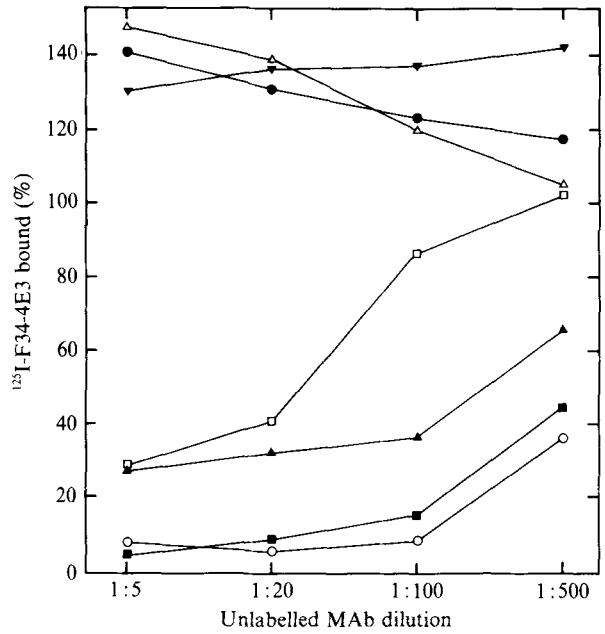

Fig. 2. Competitive inhibition of binding of ^{125}I-labelled MAb F34-4E3 to 1605L cells in the presence of excess concentrations of several other unlabelled gp350/gp220-specific MAbs. △, F29-89; ●, F16-11B7; ▼, F16-3E3; □, 2F5.6; ▲, F34-4G8; ■, F29-167; ○, F34-4E3.

example of inhibition curves generated by this type of competitive binding study is shown in Fig. 2. MAb F29-167 blocked binding of the ^{125}I-labelled F34-4E3 MAb as well as the unlabelled autologous antibody over the complete range of inhibitory antibody dilutions tested. Two MAbs, F34-4G8 and 2F5.6, only blocked effectively at the two higher concentrations of the unlabelled MAbs and pre-incubation with the other three MAbs actually enhanced the binding of the ^{125}I-labelled F34-4E3. This enhanced binding was not seen routinely; in fact, it was unique for only a select group of MAbs all clustering within a single epitope (see Discussion). This type of competitive binding analysis was completed for all the MAbs in the study. When the MAbs displaying strong reciprocal blocking were placed into separate groups, the epitope 'map' shown in Table 2 was the result. Seven distinct epitopes are indicated. Epitope group I has eight MAbs which showed reciprocal cross-blocking, groups II, III and IV each have only one MAb and groups V to VII contain two or three MAbs. Close inspection of this Table reveals several interesting observations. Epitope groups I and II show considerable similarities, but the group II MAb must certainly be recognizing an epitope distinct from the eight MAbs of group I, since it recognized an epitope on B95-8 cells, but not on the P_3HR-1 cell line (Qualtiere *et al.*, 1982*b*), while all of the group I MAbs recognized both prototype producer lines equally well. Epitope groups VI and VII likewise showed, although at a significantly lower level, a limited degree of cross-blocking among both groups, but the only strong reciprocal cross-blocking was seen by members within each group. The MAb in epitope groups VI and VII clearly blocked only each other well and the single MAbs in groups III and IV only showed reciprocal blocking with the autologous antibody. It was tempting to place MAb F16-3E3 and F29-89 into a single epitope group since partial blocking of F16-3E3 was seen repeatedly when F29-89 was used as a blocking antibody. However, even at very high inhibitory concentrations, F16-3E3 was never seen to block the binding of F29-89. Stringent interpretation of this non-reciprocal blocking therefore places each MAb into a separate epitope group.

Table 2. *Epitope map of EBV gp350/220*

Epitope group		F30-3C2	F34-4G8	F34-4E3	F29-167	F34-1F2	F34-5D3	F34-6B5	F34-6B1	2F5.6	F16-3E3	F29-89	F30-3C6	F16-11B7	F16-1C10	F34-5H7	F34-2B11	F30-5C8	F34-1D8
I.	F30-3C2	+4*	+3	+3	+4	+4	+3	+4		+1	–	–		–	–			–	–
	F34-4G8	+4	+4		+4	+4	+4	+4		+2	–	–		–	–				
	F34-4E3	+4	+2	+4	+3	+4	+3	+4		+2	–	–		–	–				
	F29-167	+4	+	+3	+3	+4		+4		+1	–	–		–	–				
	F34-1F2	+4	+3	+4	+4	+3	+4	+4		+2	–	–	–	–	–			–	–
	F34-5D3	+4			+4		+4		+4	–	–	–	–	–	–			–	–
	F34-6B5			+3	+2		+2		+1	–	–			–	–			–	–
	F34-6B1	+4		+4	+4		+4		+4	+2	–	–	–	–	–	–	+1		–
II.	2F5.6	+4		+4	+4	+3		+4	+4	+2	–	–	–	–	–	–	–	–	+2
III.	F16-3E3	–	–	–	+1	–	–	–		–	+4	+2	–	+1	+1	–	+	–	–
IV.	F29-89	–	–	–	–	–		–			–	+4	–	–	–	–	–	–	–
V.	F30-3C6	–	–	+1	–	+	–			–		–	+3	+3	+2	+	+2	–	–
	F16-11B7	–			–	–					–	+1	+2	+4	+3	+2	+2	+1	+
	F16-1C10	–			–		–			–	–	–	–	+4	+4	–	+1	–	+2
VI.	F34-5H7	–				–		+1		–	–	–	–	+2	–	+3	+4	–	+1
	F34-2B11	–				–		–		–	–	–	–	+2	–	+3	+4	–	+1
VII.	F30-5C8	–		–		–		–	–	–	–	–	–	–		–	–	+4	+4
	F34-1D8	–		–		–		–		–	–	–	–	–		–	–	+2	+2

* Relative degree of inhibition of ^{125}I- or FITC-labelled antibody binding to TPA-activated B95-8 cells by a 50-fold excess of unlabelled antibody. +4, 100 to 80%; +3, 80 to 60%; +2, 60 to 40%; +1, 40 to 20%; +, 20 to 10%; –, >10%.

Table 3. *Neutralization of EBV infectivity by MAbs specific for gp350/220*

Epitope group		Inhibition of cord blood transformation by MAbs*	
		− Complement	+ Complement
I.	F29-167	++	++
	F30-3C2	±	±
	F34-5D3	−	+
	F34-1F2	±	++
	F34-6B5	−	−
II.	2F5.6	−	−
III.	F16-3E3	−	−
IV.	F29-89	+	++
V.	F16-11B7	−	−
	F16-1C10	−	−
VI.		NT†	NT
VII.		NT	NT

* Transformation was prevented in at least three of four cultures at an antibody dilution $\leqslant$ 1:1000 (++), $\leqslant$ 1:100 (+) or 1:10 (±); −, no neutralization.

† NT, Not tested.

Neutralization of EBV infectivity

To determine if any of the seven epitope groups elicited a strong neutralizing antibody response, all of the mapped MAbs were tested for their ability to inhibit B95-8 virus transformation of umbilical cord lymphocytes both in the presence or absence of complement. The results are shown in Table 3. Four MAbs within group I displayed neutralizing activity as well as the group IV MAb F29-89. MAb F34-5D3 was neutralizing only when complement was present and the neutralizing activity of F29-89 and F34-1F2 was significantly enhanced in the presence of complement.

DISCUSSION

Development of a truly effective subunit vaccine using EBV membrane glycoproteins requires the identification of the epitopes capable of eliciting a protective immune response to the virus. Certainly, in any initial attempts to formulate an effective subunit vaccine, biologically important epitopes capable of generating neutralizing antibodies should be included. Since several previous studies (Qualtiere *et al.*, 1982*a*; Thorley-Lawson & Geilinger, 1980; Thorley-Lawson & Poodry, 1982) had shown the importance of the major outer membrane glycoprotein gp350/220 in eliciting protective antibodies, we began to map immunochemically the epitopes on this molecule with a battery of 18 IgG mouse MAbs directed against this antigen. Competitive blocking studies using these 18 MAbs demonstrated that gp350/220 has at least seven distinct antigenic epitopes which can be recognized by mice immunized with MA-expressing cells (Table 2). Two of these epitopes were also clearly shown to elicit a neutralizing antibody capable of preventing transformation by B95-8 virus of cord blood lymphocytes (Table 3). Preliminary observations based on this limited number of MAbs would seem to suggest that epitope group I, containing eight of the 18 MAbs found in this study, is the major epitope of the gp350/220 molecule and is also clearly capable of generating neutralizing antibodies *in vivo*. This observation is further strengthened by the mapping of the previously described neutralizing MAb 72A1 (Hoffman *et al.*, 1980) to this epitope group (unpublished observation).

That only one of the other MAb groups tested was also capable of generating a neutralizing antibody response must be interpreted carefully, since it was shown that even within the group I MAbs a wide variation was seen between their abilities to neutralize B95-8 infectivity. The further cataloguing of more MAbs within the now seven specified epitopes might show that most of the epitopes may produce a neutralizing antibody response. It is only when six or seven MAbs against each epitope can be tested that we will be able to establish firmly whether or not

any particular epitope has the potential to induce a neutralizing antibody response. Certainly, the observation that the largest number of MAbs to gp350/220 are in epitope group I may indicate that the epitope recognized by the group I MAbs is immunodominant and biologically important in the induction of protective neutralizing antibody.

Another observation generated from this study which would also tend to support the contention that epitope group I may be important with regard to EBV infectivity is illustrated by the enhancement phenomena seen in Fig. 1. Clearly, several of the MAbs in this study had the ability to enhance the binding of other MAbs through prior binding to the antigen. Analysis of this enhancement phenomenon revealed that only epitope group I MAbs (six of eight) had their binding enhanced in this manner. Further, only epitope groups III, IV, V and VI were capable of mediating the enhancement (groups II and VII were not). Finally, epitope group I MAbs did not enhance the binding of any of the other epitope groups. This enhanced binding of one MAb by another has been seen in other studies (Lemke & Hämmerling, 1982; Parham *et al.*, 1982) and is not understood as yet. Perhaps the best explanation is that prior binding of one MAb may 'hold' through cross-linking the membrane glycoprotein in a particular spacial configuration that allows additional binding by antibodies to other epitopes not accessible except at this particular steric arrangement. Whether this enhancement phenomenon functions during *in vivo* neutralization of EBV is difficult to predict. Nonetheless, the observation may suggest a biological mechanism in which synergistic antibody binding to various epitopes other than epitope group I may promote antibody-mediated destruction of the virus particle by enhancing antibody binding to epitope group I.

Clearly, the next step in the study of EBV gp350/220 will be to determine the actual amino acid composition of the epitopes recognized by the group I and possibly group IV MAbs. The synthesis of peptides spanning those epitopes should then permit their evaluation as potential immunogens in a truly effective subunit vaccine to EBV.

All the MAbs reported in this paper will be made available to any interested party upon written request to the senior author (L.F.Q.).

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