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Immune Reactivity of the Purified Hemagglutinin of Measles Virus

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The role of the immune response to measles virus in acute infection or in disease states associated with this virus is of major interest. The viral genome-specified surface antigens of measles, the hemagglutinin and fusion proteins, are likely to be of paramount importance with respect to the host immune response to the virus. This report describes initial studies aimed at assessing the immune response to the major surface glycoprotein, the hemagglutinin. This antigen was purified by affinity chromatography, using a monoclonal anti-hemagglutinin immobilized on Sepharose. The purified protein retained biological activity in hemagglutination assays. This activity could be specifically inhibited with a human antimeasles serum and with monoclonal antibody to the hemagglutinin. Lymphocytes from individuals known to proliferate to measles-infected monolayers also proliferated to the purified hemagglutinin. Thus, the immune response to measles virus is, in part, directed to this surface antigen.

Measles virus is a ubiquitous infectious agent of humans of considerable biological importance. In most natural infections, the virus produces a self-limiting disease culminating in long-term immunity. This same paramyxovirus, however, is associated with a persistent infection which leads to a progressive neurological disease, subacute sclerosing panencephalitis (SSPE) (1, 7).

Much attention has been focused on the differences in antibody responses to the polypeptides of the virus in normal individuals compared with patients with SSPE (6, 18, 20). In contrast, little information is available on the cellular response to this virus. Recent studies have compared the cell-mediated immune response to measles virus with that of mumps and vaccinia viruses in lymphoproliferative assays. Although substantial responses were observed in immune individuals to mumps and vaccinia viruses, only a small number (6 of 150) of measles-seropositive individuals responded to measles virus (13). Preliminary studies have shown that some of these same individuals are capable of generating measles-specific killer cells in cytoxicity assays (C. J. Lucas, D. L. Nelson, H. F. McFarland, and S. Shaw, Proc. Int. Congr. Immunol. 4th, Brionne, France, abstr. no. 9.2.12, 1980).

One deterrent to studying the immune response to any virus is the number and complexity of antigens involved in the response. The primary targets in the recognition and effector phases of the immune response to measles virus are the viral genome-encoded surface antigens, the hemagglutinin (HA) and fusion (F) proteins (4). This report describes the purification of the major surface antigen of measle virus, the HA protein, and its reactivity with antibody and human peripheral blood lymphocytes. The availability of this purified antigen should facilitate the examination of the cell-mediated immune response to measles virus and the elucidation of the mechanisms which control the response.

MATERIALS AND METHODS

Cell culture and maintenance. Monolayers of MA-160 SSPE cells, a human prostate cell line persistently infected with the Mantooth strain of measles virus (M. A. Bioproducts, Walkersville, Md.), were grown in Eagle minimal essential medium (GIBCO Laboratories, Grand Island, N.Y.) containing 5% fetal calf serum. Each 100 ml of medium was supplemented with 2.0 ml of 100× vitamins, 1.0 ml of nonessential amino acids, 100 μg of penicillin, and 100 μg of streptomycin (GIBCO). Cell cultures were maintained in a humidified atmosphere of 5% CO_2 in air at 37°C.

Radiolabeling of cells. Surface iodination was performed as previously described (5). The ^{125}I surface-labeled MA-160 SSPE cells were lysed by Dounce homogenization after being swollen in reticulocyte standard buffer for 15 min. To ensure that only surface proteins were labeled, lysates containing both cytoplasmic and membrane components were immunoprecipitated with measles antiserum containing antibody to internal and surface polypeptides (3). Only surface polypeptides were detected when immunoprecipitates were assessed by sodium dodecyl sulfate-polyacryl-

amide gel electrophoresis (SDS-PAGE) and autoradiography.

Plasma membrane isolation. Surface-iodinated MA-160 SSPE cells (1.2×10^7) were mixed with unlabeled cells (5×10^8) and Dounce homogenized in reticulocyte standard buffer. After removal of nuclei, crude membranes were pelleted by ultracentrifugation, suspended in 1 mM tris(hydroxymethyl)-aminomethane (Tris)-hydrochloride, pH 8.0, and 1 mM ethylenediaminetetraacetic acid (EDTA), and again pelleted. Membranes were suspended in 55% (wt/wt) sucrose and further fractionated by flotation in discontinuous sucrose gradients as described (9). After centrifugation, six pooled fractions of decreasing density were made on the basis of location of light-scattering material and the corresponding radioactive peak fractions along the gradient. Membranes from each pool were pelleted, and the protein composition of each was determined by SDS-PAGE. The nomenclature of Knipe et al. (9) was used for identification of these fractions.

Smooth membrane fractions containing the majority of the HA protein were solubilized in RIPA buffer (11) containing 0.01 M Tris-hydrochloride, pH 7.4, 0.15 M NaCl, 0.1 % SDS, 1.0 % (wt/vol) sodium deoxycholate, 1 % (wt/vol) Triton X-100, 2 mM phenylmethylsulfonyl fluoride, and 5×10^6 U of Aprotinin per ml (Sigma Chemical Co., St. Louis, Mo.). This buffer was found to solubilize membrane proteins and to preserve the immunological reactivity of measles HA with antibody (14). In some experiments, the method described was used to obtain membrane fractions from unlabeled uninfected as well as infected MA-160 cells.

Anti-HAS. The C-2 clone (14), which produces monospecific antibody (immunoglobulin G1 [IgG1K]) against the HA protein, was injected into BALB/c mice pretreated with pristane. Immunoglobulin from the resulting ascitic fluids was precipitated with saturated ammonium sulfate and further purified by diethylaminoethyl-cellulose chromatography. Each fraction was analyzed by double diffusion in agar, using rabbit anti-mouse IgG and goat anti-mouse serum, and by radioimmunoassay for anti-HA activity (14). Fractions containing only IgG and anti-HA antibody were pooled and dialyzed against Dulbecco phosphate-buffered saline. The anti-HA pool containing 21.8 mg of IgG was coupled to 22 ml of cyanogen bromide-activated Sepharose 4B (2). The efficiency of this reaction was 88%. The resulting anti-HA immunoabsorbent (anti-HAS) was washed with 0.1 M glycine, pH 2.8, followed by 0.2 M borate-buffered saline, pH 8.0, containing 0.1% azide and stored in the latter buffer at 4°C.

Purification of measles HA. Anti-HAS (2.0 ml of packed Sepharose) was placed in a 5.0-ml syringe and equilibrated with RIPA buffer. Membrane fractions solubilized in the same buffer were passed over the column at a rate of 1.0 ml/10 min. The column was washed with 10 column volumes of RIPA followed by a similar quantity of 10 mM Tris-hydrochloride, pH 8.0, 1 mM EDTA, and 0.1 % Nonidet P-40. The adsorbed HA protein was eluted from the column by using the latter buffer containing 3.0 M potassium thiocyanate. The eluted protein was dialyzed against phosphate-buffered saline at 4°C.

PAGE. SDS-PAGE slab gels (9.0 %) were prepared as previously described (10). Gels were fixed and stained with Coomassie brilliant blue, destained, and dried under vacuum. Autoradiography was performed with Kodak XR-2 X-ray film at −70°C.

HA and HAI. HA and HA inhibition (HAI) assays were performed according to a previously described procedure (8). A commercial measles antigen preparation (M. A. Bioproducts) was used as the standard in assays examining the HA activity of the purified HA protein. HAI titers are expressed as that dilution of serum resulting in complete inhibition of rhesus monkey erythrocyte agglutination. For these studies, an SSPE serum containing antibody to all measles polypeptides (W. J. Bellini, G. D. Silver, E. S. Mingioli, H. F. McFarland, and D. C. McFarlin, unpublished data), monoclonal anti-HA ascites fluid, and control ascites fluid from mice given P3 × 63 Ag8 myeloma cells used in the fusion that generated anti-HA (14) were used.

Lymphocyte proliferation. Human peripheral blood lymphocytes from donors known to be consistently high or consistently low responders to measles-infected monolayers were isolated by Ficoll-Hypaque centrifugation (13). Lymphocytes (3×10^5/well) were cultured in RPMI 1640 (GIBCO) with 1 % AB serum and antibiotics. Lymphocytes from both high- and low-responding individuals to measles virus responded to mitogens. Antigens consisted of glutaraldehyde-fixed (0.025% for 20 min) monolayers of persistently infected or uninfected MA-160 cells, plasma membranes prepared from infected or uninfected cells (described above), or purified HA antigen. The HA protein comprised approximately 10 to 20% of the total protein of MA-160 SSPE plasma membranes (see Results). Thus, protein concentrations of the purified HA antigen used in lymphoproliferative assays were approximately one-tenth to one-fifth of the plasma membrane protein concentrations used in the assays. Each variable was studied in triplicate. After 96 h of culture, the wells were pulse-labeled with 1 μCi of [^{3}H]thymidine for 4 h and harvested on a MASH II harvester. The incorporation of [^{3}H]thymidine was measured by liquid scintillation spectrometry.

RESULTS

The MA-160 SSPE cell line was chosen for this study because it exhibited strong hemadsorption activity with rhesus monkey erythrocytes. Moreover, virtually every cell had HA protein on the membrane surface when examined by immunofluorescence with monoclonal antibody to measles HA (14). Synthesis of the HA protein occurs in association with membrane-containing organelles and is present in a fully glycosylated state in plasma membranes (Bellini et al., manuscript in preparation). Thus, to obtain the HA antigen in a form most closely representing that which the immune system would encounter, plasma membrane-enriched fractions of the MA-160 SSPE cells were used as starting material for the purification.

Figure 1 presents a typical SDS-PAGE profile

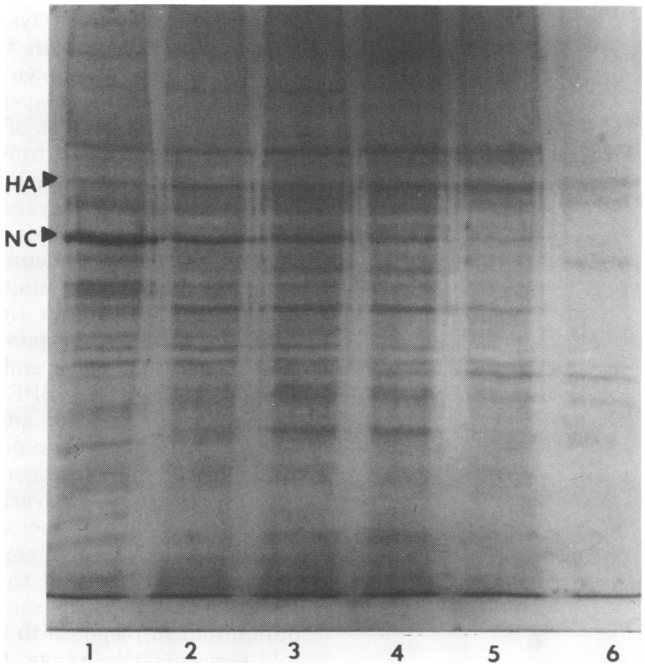

FIG. 1. *Coomassie brilliant blue-stained SDS-PAGE (9% slab) patterns of sucrose gradient-fractionated membrane components of MA-160 SSPE cells. Appropriate fractions from sucrose gradients were pooled, pelleted, and solubilized in 2% SDS and 5% β-mercaptoethanol. Equal volumes of individual fractions were applied to the gels for relative protein compositions. Densities (grams per milliliter) are: (1) 1.25; (2) 1.21; (3) 1.185; (4) 1.17; (5) 1.135; (6) 1.11. NC, Nucleocapsid.*

of the protein components present within the various membrane fractions of MA-160 SSPE cells. A protein with a molecular weight of 76,000, corresponding to the molecular weight of measles HA (3, 15, 19), was present in greatest quantity in the plasma membrane-enriched fractions (bands 4 through 6). These fractions also contained the majority of the ^{125}I surface-labeled components. Very little of this 76,000-dalton component was observed in the most dense fractions containing the rough endoplasmic reticular membranes (bands 1 and 2). Measles nucleocapsid protein (molecular weight of 60,000) was enriched in these fractions, consistent with the density of the viral ribonucleic acid-nucleocapsid protein structures (15). This protein was essentially absent from the plasma membrane-enriched fractions.

Solubilized membrane components from fractions 4, 5, and 6 were then passed over the anti-HAS column. Protein bound by the column eluted as a sharp peak of radioactivity (fractions 52 through 56) which represented 20% of the total radioiodinated material applied to the column (Fig. 2). This material was dialyzed and analyzed on SDS-PAGE (Fig. 3, lanes 3 through 5). Both Coomassie brilliant blue staining and autoradiography revealed the presence of a single polypeptide component with a molecular weight of 76,000, consistent with that of the measles HA. The polypeptide components of the starting material and of the material which did not bind to the affinity columns were compared by SDS-PAGE, using equivalent protein concentrations from each fraction (Fig. 3, lanes 1 and 2). Densitometric determinations indicated that greater than 90% of the HA protein was removed from the starting material by the anti-HAS column; otherwise, the polypeptide compositions of the fractions were identical. Essentially all of the HA bound to the affinity column was subsequently recovered by elution with the chaotropic salt.

Biological activity of purified HA. The purified 76,000-dalton peptide was assessed for HA activity with rhesus monkey erythrocytes. Serial twofold dilutions of the purified protein beginning with 12 μg/ml were examined in standard HA assays. Positive agglutination was observed at a 1:64 dilution, corresponding to a final HA protein concentration of 20 ng. Commercial antigen preparations assayed in parallel resulted in HA titers of 1:64 as well.

It has been reported that a complex of monomeric HA is necessary for agglutination of erythrocytes (16). Thus, the purified HA preparation

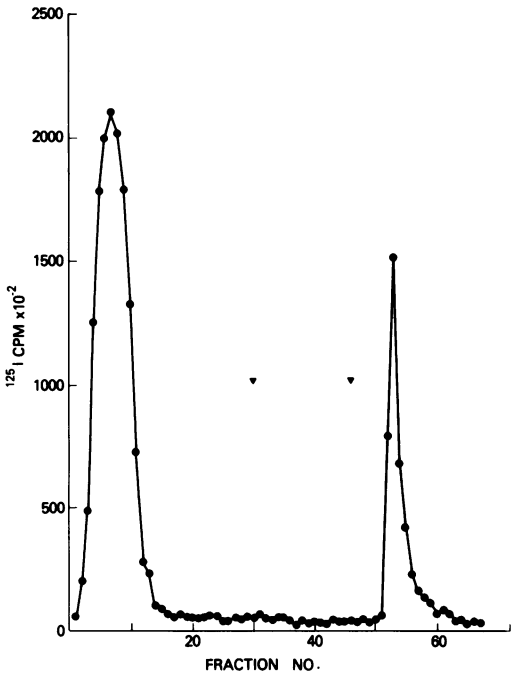

FIG. 2. *Elution profile of ^{125}I surface-labeled proteins from the anti-HAS affinity column. Membrane fractions (4–6, Fig. 1) were solubilized in RIPA buffer and passed over the anti-HAS column as described in Materials and Methods. Arrows (left to right) indicate the column buffer changes from RIPA to Tris-EDTA plus 0.1% Nonidet P-40 and from the latter buffer to the 3.0 M potassium thiocyanate elution buffer, respectively. Radioactive peaks (left to right) represent the unbound material and the eluted HA, respectively.*

was examined for the presence of aggregates by velocity sedimentation through 5 to 30% (wt/wt) sucrose gradients. Relative to the marker protein, IgG (7S), the majority of the HA protein (70%) migrated as aggregates greater than 20S, whereas the remainder sedimented as 7 to 10S material. Assuming an S value of 3 to 4 for a 76,000-dalton globular protein, none of the purified HA sedimented as a monomer.

Antibody reactivity of purified HA. The capacity of the purified HA to react with antibody was measured in HAI assays. For HAI, a dilution of the purified HA containing 4 HA units was reacted with serial 10-fold dilutions of either ascites fluid containing monoclonal anti-HA, control ascitic fluids, or an SSPE serum. Specific anti-HA activity was obtained with both the monoclonal anti-HA and the SSPE serum with respective HAI titers of 1:100 and 1:1,000. Control ascites fluid resulted in no inhibition.

Cellular response to purified HA. The response to purified HA antigen was assessed in lymphoproliferative assays. Lymphocytes from three individuals known to respond well and from six individuals known to respond poorly to measles-infected monolayers (13) were studied. Table 1 shows examples of the proliferative response of lymphocytes from two high- and two low-responding individuals to measles-infected MA-160 SSPE monolayers. Table 2 shows the responses of lymphocytes from these same individuals to plasma membranes derived from infected or uninfected monolayers as well as to the purified HA protein. Lymphocytes from individuals known to respond to infected monolayers (Table 2, no. 1 and 3) significantly responded to MA-160 SSPE plasma membranes over a broad range of antigen concentration. Lymphocytes from these donors also responded to the purified HA antigen. The magnitude of this response, however, varied with respect both to that observed with membranes from infected cells and to HA protein concentration. Donor 3 responded equally well to the MA-160 SSPE membranes and to the purified HA, with little diminution in response to the latter over a 50-fold concentration range. In contrast, donor 1 consistently responded to a greater degree to the plasma membranes from infected cells than to the purified HA antigen. The response to the HA protein diminished rapidly upon dilution of the antigen. The response of the third high-responding individual resembled that of donor 1 (data not shown).

Lymphocytes from donors known to minimally respond to measles-infected monolayers (no. 2 and 4) also responded poorly to membranes derived from infected cells and the purified HA antigen. In five separate experiments using two different preparations of the HA protein, it was consistently observed that lymphocytes from three donors known to respond to measles-infected monolayers also responded to membranes from infected cells and the purified surface component of measles virus, the HA protein. The converse relationship was observed with lymphocytes from six donors which responded poorly to measles-infected monolayers.

DISCUSSION

Two surface proteins are encoded for by the genome of measles virus. These polypeptides are present in plasma membranes of infected cells and in the envelope of the virus. The surface antigens probably represent the primary targets for immune recognition in vivo. To examine more closely the immune response to these antigens, we have successfully purified the major surface antigen of measles virus, the HA protein.

The purified HA protein retained HA activity

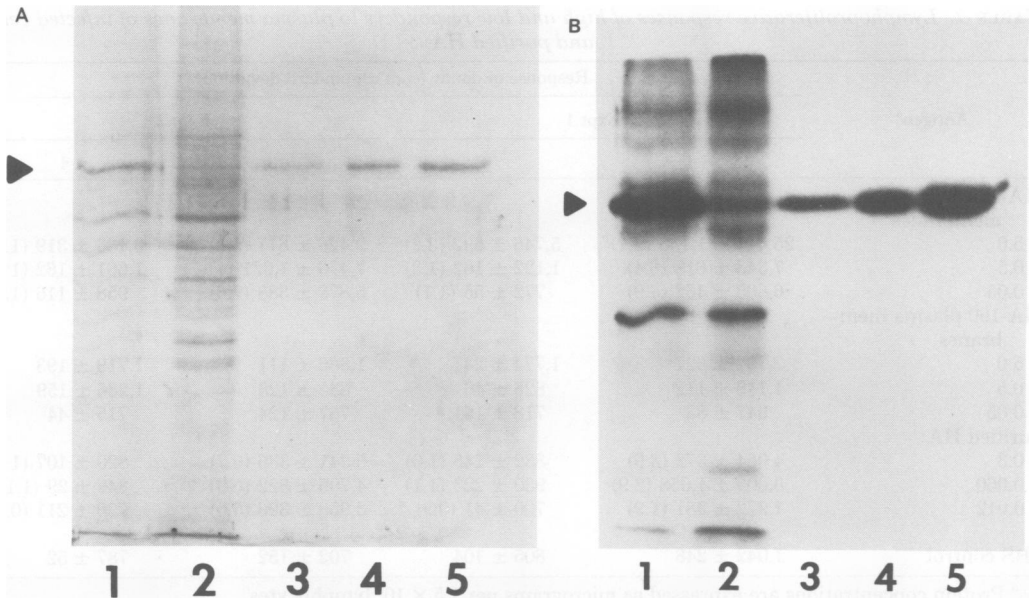

FIG. 3. *SDS-PAGE (9%) gel patterns of: (1) pooled membrane fractions applied to the anti-HAS column (50 μg of protein; 10,000 ^{125}I cpm); (2) membrane protein components not bound by anti-HAS column (50 μg of protein; 10,000 ^{125}I cpm); (3–5) increasing amounts of the eluted HA after dialysis against phosphate-buffered saline (0.5, 1.0, and 1.5 μg of protein; 870, 1,650, and 2,560 ^{125}I cpm, respectively). (A) Coomassie brilliant blue-stained gel. Stainable material appearing below the HA protein is an artifact that often is observed in gels when samples contain nonionic detergents. (B) Autoradiograph of the same gel (3-day exposure). Arrow indicates the migration of immunoprecipitated measles HA in reference gels.*

TABLE 1. *Lymphoproliferative responses of high and low responders to measles-infected monolayers*

Antigen[a]	Response of donor (cpm ± standard deviation)			
	1	2	3	4
MA-160 SSPE	19,506 ± 2,172 (16.6)[b]	850 ± 92 (2.2)	12,729 ± 1,182 (17.3)	1,732 ± 331 (3.1)
MA-160	1,171 ± 42	392 ± 61	734 ± 139	544 ± 82

[a] Infected or uninfected cells grown in 96-well plates as monolayers.

[b] Value in parentheses is stimulation index, calculated by dividing cpm of infected monolayers by cpm of uninfected monolayers.

when reacted with rhesus monkey erythrocytes. Agglutination of erythrocytes has been shown to be dependent on the presence of aggregates in preparations of purified influenza virus HA (12, 17). Similarly, when the purified measles HA was analyzed by velocity sedimentation, aggregates (>20S) were detected. Such aggregates provide a means for cross-linking erythrocytes, thus giving rise to the HA activity. Presumably monomeric HA would lack this biological activity.

Structural conformation is believed to contribute significantly to those antigenic determinants which react with antibody. It is possible that such properties might be altered during the purification of a protein antigen, particularly when detergents are used. Both monoclonal anti-HA and SSPE serum capable of inhibiting the biological activity of the HA. This result indicates that at least those antigenic determinants of the HA protein which react with antibody to specifically inhibit HA activity are conserved throughout the purification method.

In experiments designed to examine the cellular response to measles virus, lymphocytes from individuals known to respond well or poorly to infected monolayers were used. Lymphocytes from six individuals previously shown to be low responders also did not respond to either membranes from infected cells or the purified HA protein. In contrast, lymphocytes from three high responders gave a significant response both to membranes from infected cells and to the purified antigen. These findings demonstrate that the lymphocyte response to measles-infected monolayers is directed to antigens

TABLE 2. *Lymphoproliferative responses of high and low responders to plasma membranes of infected cells and purified HA*

Antigen[a]	Response of donor (cpm ± standard deviation)			
	Expt 1		Expt 2	
	1	2	3	4
MA-160 SSPE plasma membranes				
5.0	25,444 ± 1,168 (9.1)[b]	5,746 ± 692 (3.2)	9,426 ± 811 (5.0)	3,136 ± 319 (1.8)
0.5	7,343 ± 618 (6.4)	1,122 ± 162 (1.3)	7,476 ± 1,021 (11.7)	1,661 ± 162 (1.3)
0.05	6,605 ± 462 (6.9)	772 ± 55 (1.1)	5,878 ± 388 (7.6)	958 ± 116 (1.3)
MA-160 plasma membranes				
5.0	2,792 ± 627	1,774 ± 247	1,886 ± 111	1,719 ± 193
0.5	1,148 ± 112	826 ± 46	635 ± 128	1,286 ± 159
0.05	947 ± 83	718 ± 161	767 ± 124	715 ± 44
Purified HA				
0.3	4,054 ± 372 (3.9)	832 ± 145 (1.0)	5,341 ± 336 (6.7)	820 ± 107 (1.0)
0.060	3,005 ± 1,058 (2.9)	930 ± 223 (1.1)	4,796 ± 822 (6.0)	846 ± 29 (1.1)
0.012	1,972 ± 381 (1.9)	700 ± 41 (0.9)	3,958 ± 396 (5.0)	730 ± 211 (0.9)
PBS control	1,042 ± 248	805 ± 104	702 ± 152	787 ± 52

[a] Protein concentrations are expressed as micrograms per 1.5×10^6 lymphocytes.

[b] Values is parentheses are stimulation indices, calculated for plasma membranes by dividing cpm of infected monolayers by cpm of uninfected monolayers and for HA protein by dividing cpm of purified HA by cpm of phosphate-buffered saline (PBS) control.

present within the plasma membranes of infected cells. The response of lymphocytes from donor 3 (Table 2) to the purified HA protein paralleled that obtained with membrane antigens from infected cells, which indicates that a major component of the cellular response, as measured by this assay, is directed at the HA antigen. In the other two responders, a significant response against the HA protein was detected; however, this was less than that obtained with either the membrane fractions from infected cells or infected monolayers. Thus, in these individuals the cellular response may be directed at the other surface antigen, the F protein, or to a determinant made up of the HA and F proteins. Alternatively, the aggregated state of the HA protein may mask certain determinants necessary for optimal antigen presentation and immune recognition.

Further evaluation of these possibilities would obviously benefit by the identification of more individuals whose lymphocytes respond to measles, as well as by the purification of the F polypeptide. The availability of the purified, antigenically active HA protein should allow more incisive investigation of the determinants important for T-cell recognition and insight into the regulation of the immune response to this virus.

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