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Immunology

Molecular mimicry in virus infection: Crossreaction of measles virus phosphoprotein or of herpes simplex virus protein with human intermediate filaments

(monoclonal antibodies/vimentin/autoantibodies)

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ABSTRACT **Using monoclonal antibodies, we demonstrate that the phosphoprotein of measles virus and a protein of herpes simplex virus type 1 crossreact with an intermediate filament protein of human cells. This intermediate filament protein, probably vimentin, has a molecular weight of 52,000, whereas the molecular weights of the measles viral phosphoprotein and the herpes virus protein are 70,000 and 146,000, respectively. Crossreactivity was shown by immunofluorescent staining of infected and uninfected cells and by immunoblotting. The monoclonal antibody against measles virus phosphoprotein did not react with herpes simplex virus protein and vice versa, indicating that these monoclonal antibodies recognize different antigenic determinants on the intermediate filament molecule. The significance of these results in explaining the appearance of autoantibodies during virus infections in humans is discussed.**

Many mechanisms have been proposed to account for the induction of autoimmunity in humans. One plausible explanation is infection by virus. Viruses may induce autoimmune responses through shared determinants on molecules normally present on host cells, by altering the host immune system, or by causing the expression or release of "normally sequestered" self antigens. Autoantibodies are a frequent finding in the sera of virus-infected individuals, both during and after infection. For example, after infection with Epstein–Barr virus (1, 2), antibodies reacting with intermediate filaments of cells, immunoglobulin, or thyroglobulin were detected. Similarly, humans infected with hepatitis, herpes, mumps, or measles viruses can develop antibodies to their own cytoskeletal components (3–5), although the antibodies that reacted with cytoskeletal proteins were not shown to bind to viruses (5).

Monoclonal antibodies (MAbs) provide probes to analyze unique determinants on viruses and on self constituents. Using such probes, we have described (6, 7) a MAb against herpes simplex type 1 virus (HSV-1) that reacts with a variety of uninfected mammalian cells. Furthermore, we have noted that a large proportion of MAbs originally derived by immunization of mice with measles virus polypeptides react with self constituents of human cells. We describe here two MAbs with dual specificity; one recognizes the phosphoprotein of measles virus and the intermediate filament protein, M_r 52,000. The other binds to and immunoprecipitates a protein present during the late phase of HSV infection (7) and reacts with a similar intermediate filament protein. The intermediate filaments are a normal component of uninfected cells.

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MATERIALS AND METHODS

Cells, Virus, and Virus Infection. HeLa, Vero, BHK_{21}, CV-1, HEp-2, and human astrocyte cells were maintained in Eagle's minimal essential medium containing 10% fetal calf serum, 1% glutamine, and antibiotics. These cells were cultured in T75 flasks (Falcon) at 37°C in 5% CO_2 and passed twice weekly. Astrocytes derived from a human brain biopsy sample were positive for glial fibrillary acidic protein by immunofluorescent staining.

P3X63Ag8 mouse plasmacytoma cells (P3) were grown in Eagle's medium containing 10% fetal calf serum and 0.1 mM 8-azaguanine. Supernatants obtained from plasmacytoma cell cultures were used as negative controls for the fluorescence antigen detection and immunoblotting. Cloned hybridomas producing antibody to the measles virus nucleocapsid were from E. Norrby (Karolinska Institute, Stockholm) and those producing antibodies to the hemagglutinin were from D. McFarlin (National Institutes of Health, Bethesda, MD). All other measles and HSV MAbs were generated after immunization of BALB/c mice with either measles virus (8, 9) or HSV-1 (7) and fusion of mouse splenocytes with mouse myeloma cells according to the technique described previously (10). The preparation, purification, and use of either measles virus (Edmonston strain) or HSV-1 (F strain) to infect cells and the subsequent radioimmunoassay, immunofluorescence, and $NaDodSO_4$/polyacrylamide gel analysis have been reported (7, 9, 11).

Cytoskeleton Preparation. A preparation of Triton-X-100-insoluble proteins (intermediate filament-enriched) of HeLa cells was obtained as described by Pruss *et al.* (12).

Gels, Immunoprecipitation, and Immunoblotting. $NaDodSO_4$ gels were analyzed as described (8, 9). Immunoprecipitation was performed as described by Frankel *et al.* (7). Proteins from gels were transferred to nitrocellulose paper (Schleicher & Schuell) as reported by Towbin *et al.* (13). Strips were incubated with 5 ml of supernatant fluid from hybridoma or P3 cell culture (8), in 5 ml of 3% bovine serum albumin/0.1% deoxycholic acid/0.5% Nonidet P-40/1% normal goat serum in phosphate-buffered saline (binding buffer), or 20 μl of ascitic fluid derived from BALB/c mice injected with the hybridoma cells in 10 ml of binding buffer. The strips were then incubated for 1 hr at 37°C, washed three times with 3% bovine serum albumin in phosphate-buffered saline, and incubated with 10 ml of binding buffer containing 1×10^6 cpm of ^{125}I-labeled goat anti-mouse Ig. Affinity-purified goat anti-mouse Ig used had been labeled with ^{125}I to a specific activity of 4 μCi/μg (1 Ci

Abbreviations: MAb, monoclonal antibody; HSV-1, herpes simplex virus type 1; P3, P3X63Ag8 mouse plasmacytoma cells.

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= 3.7×10^{10} Bq) by using Enzymobeads (Bio-Rad) and passed through a Sephadex G-25 column before use. After 3 hr at 37°C, the strips were washed three times with 10 ml of 1.5% bovine serum albumin in phosphate-buffered saline and dried overnight. Strips were mounted and exposed to Kodak X-RPI x-ray film the next day.

RESULTS

Anti-HSV-1 MAb. Antibody 37-5-1B (IgG2a), derived from hybridoma cells cloned twice by limiting dilution, bound in radioimmunoassay to purified HSV-1 preparations and to infected and uninfected BHK_{21} (hamster), CV-1 (green monkey), and HEp-2 (human) cells. It immunoprecipitated a protein of M_r 146,000 that comigrates with HSV-1 β protein ICP6 from cells labeled with [^{35}S]methionine during the late phase of viral infection (Fig. 1). MAb 37-5-1B did not neutralize HSV-1.

Detection of Crossreactivity by Immunofluorescence. The anti-measles virus MAb 2A-54-5, which reacted with measles virus-infected and uninfected HeLa cells (Fig. 2), stained uninfected cells in a pattern similar to that reported by Franke *et al.* (14) for vimentin and cytokeratins—i.e., a network-like pattern in cells with a large cytoplasm-to-nucleus ratio (Fig. 2 *A* and *B*). A network staining pattern of all cells was observed with anti-HSV-1 MAb 37-5-1B (Fig. 2*G*). In contrast, a speckled pattern of labeling was observed with 2A-54-5 in large, rounded cells and staining was concentrated between dividing cells as shown in Fig. 2 *C* and *D*. Similar patterns of reactivity with the different MAbs occurred in HeLa, Vero, and the primary human astrocytes and was cell cycle dependent. Unlike the uninfected cells, cells infected with either measles virus (Fig. 2*E*) or HSV-1 (Fig. 2*H*) showed a bright globular or diffuse staining pattern, respectively, that was more intense than the staining observed in uninfected cells. Many of the staining bodies could be seen by phase-contrast illumination as intracytoplasmic bodies (Fig. 2*F*). Upon endpoint titrations, antibodies 2A-54-5 and 37-5-1B reacted with infected cells at a 4-fold higher titer than with uninfected cells. Immunofluorescent staining of uninfected cells with MAb 2A-54-5 and 37-5-1B was seen only when cells were fixed with acetone, whereas staining of HSV-1-infected cells was seen in both fixed and unfixed cells. This suggests that MAbs react with a host-specific determinant located inside the cell.

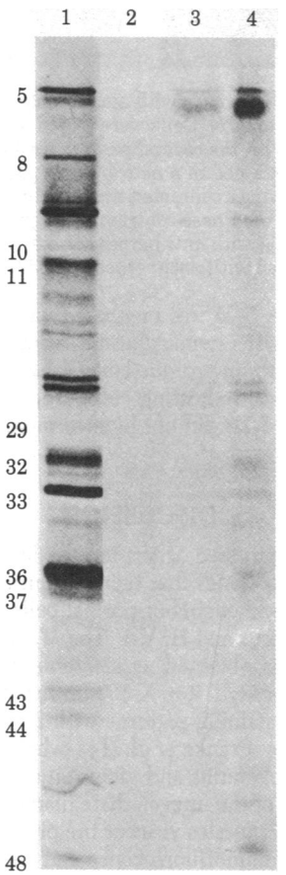

FIG. 1. Immunoprecipitation of [^{35}S]methionine-labeled HSV-1 proteins with MAb 37-5-1B. Lane 1 of the autoradiogram shows the spectrum of labeled polypeptides obtained from HEp-2 cells infected with HSV-1 (strain F) and labeled 16–21 hr after infection. Conventional numbering of several HSV-1 proteins is indicated in the left-hand margin. Labeled cell extract was incubated with 1, 10, or 50 μl of MAb 37-5-1B (lanes 2, 3, and 4, respectively). Immune complexes were removed by using a 10% suspension of *Staphylococcus aureus* (Cowan's strain), and after disruption in 10% $NaDodSO_4$ (100°C, 15 min) the soluble material was layered onto a polyacrylamide gel. The stacker and separation gels contained 3% and 9.25% acrylamide, respectively, crosslinked with *N,N'*-diallyltartardiamide. No precipitate was obtained by using [^{35}S]methionine-labeled, mock-infected cell extracts. The specific band precipitated by MAb 37-5-1B comigrates with the M_r 146,000 viral protein ICP6.

The hybridoma cell line (2A-54-5) secreting MAb was cloned by limiting dilution four consecutive times after the initial fusion. Supernatants from seven wells containing progeny of a single cell from the fourth cloning were tested for the presence of viral and cytoskeletal antibodies. Antibodies from four of the seven clones stained both infected and uninfected cells in the same pattern as described above. The other three colonies produced no detectable antibody to either HeLa cells or measles virus.

Biochemical Characterization. We first identified the cytosol component of measles virus-infected cells that MAb 2A-54-5 detected. The results are shown in Fig. 3. A band at M_r 70,000 is visible in infected cell cytosol (lane 3) but not uninfected preparations (lane 4). This band migrated with the phosphoprotein of measles virus (lane 5). Cytosols from uninfected (not shown) or infected cells failed to react with the second antibody alone or P3 supernatant fluid (lanes 1 and 2).

Because cytosol preparations contain small amounts of intermediate filaments, Triton-insoluble material (intermediate filament-enriched) from HeLa cells was prepared and electrophoresed on $NaDodSO_4$ gels. The proteins were then transferred to nitrocellulose paper and incubated with MAb specific for either measles virus phosphoprotein (3-60-5) or HeLa cytoskeleton (3-3-2), and MAb 2A-54-5 and 37-5-1B. As detected by immunofluorescence, MAb 3-60-5 reacted with infected cells in a globular pattern but not with uninfected cells, whereas MAb against HeLa cytoskeleton (3-3-2) reacted with uninfected and infected cells in the network-like staining pattern indicative of intermediate filaments. MAb 3-60-5 did not react with the Triton-insoluble preparation (Fig. 4, lane 2). MAbs 3-3-2, 2A-54-5, and 37-5-1B all reacted with a M_r 52,000 protein (Fig. 4, lanes 3, 4, and 5). Thus, MAbs 2A-54-5 and 37-5-1B (Fig. 4, lanes 4 and 5) react with the same or similarly migrating intermediate filament protein as the 3-3-2 MAb (Fig. 4, lane 3). The MAb against measles virus phosphoprotein (Fig. 4, lane 2) does not react with the M_r 52,000 protein and thus does not recognize the same determinant as 2A-54-5.

To determine whether the phosphoprotein of measles virus detected by MAb 2A-54-5 was present both in the cytoplasm of infected cells and in virions, purified measles virus was disrupted and electrophoresed on $NaDodSO_4$ gels, and the proteins were transferred to nitrocellulose paper and blotted (Fig. 5). No reaction was seen when the strip was incubated with labeled second antibody alone (lane 1), with P3 supernatant fluid

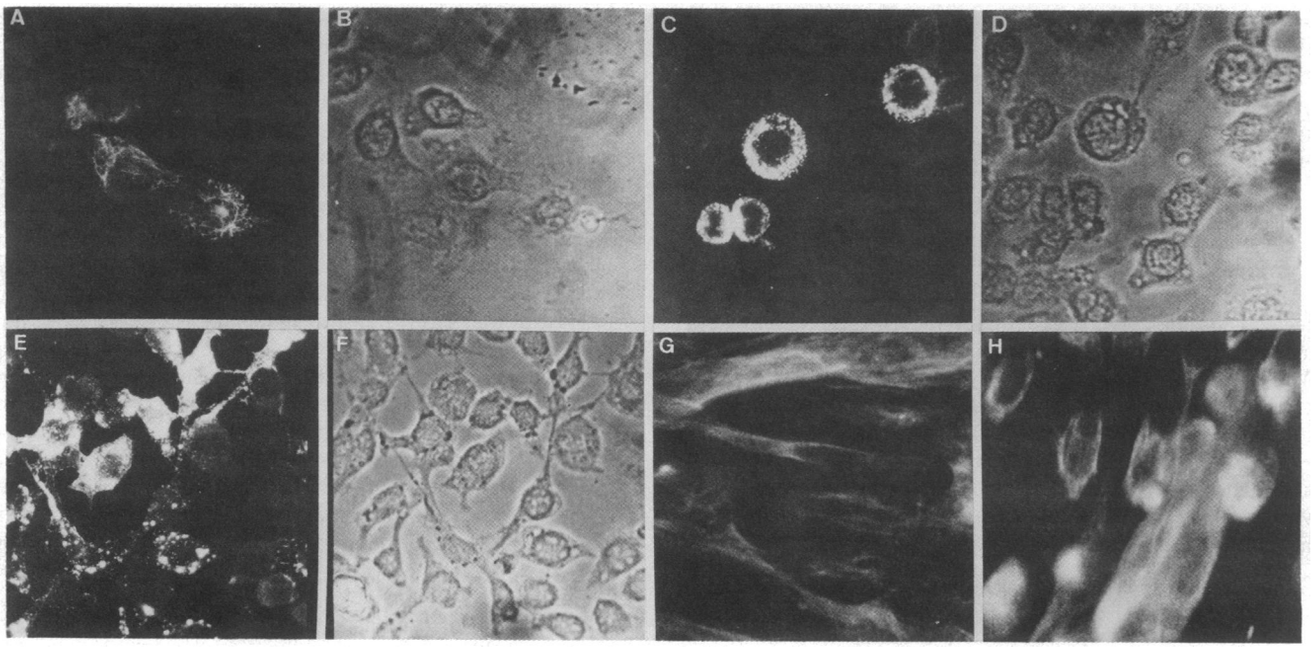

FIG. 2. Network and speckled pattern of staining of uninfected and measles virus-infected HeLa cells with anti-measles virus MAb 2A-54-5 (*A–F*) or of uninfected BHK_{21} cells and HSV-1-infected cells with anti-HSV-1 MAb 37-5-1B (*G* and *H*). Cells were plated on coverslips at a concentration of 0.5–1 × 10^5 cells per ml and infected at a multiplicity of infection of 0.5. After 24 hr, the coverslips were washed twice with warm phosphate-buffered saline and fixed with acetone. (All ×300.) (*A*) Uninfected cells spread and stained in a network-like pattern by indirect immunofluorescence. (*B*) Phase-contrast micrograph of cells in *A*. (*C*) Uninfected cells in mitosis showing a characteristic speckling. (*D*) Phase-contrast micrograph of cells in *C*. (*E*) Globular staining of the cytoplasm of measles virus-infected cells. (*F*) Phase-contrast micrograph of the same field as in *E*. Note the cytoplasmic inclusion bodies. (*G*) Network pattern staining of uninfected BHK_{21} with anti-herpes MAb 37-5-1B and (*H*) diffuse pattern of fluorescence of nucleus and cytoplasm of BHK_{21} cells infected with HSV-1 and stained with anti-herpes MAb 37-5-1B.

(lane 2), or with MAb to intermediate filament (lane 3). MAb to measles virus nucleocapsid reacted with the nucleocapsid protein (lane 4). Reaction with measles virus phosphoprotein was seen when 2A-54-5 was incubated with the strip (lane 5). MAb to measles virus hemagglutinin reacted specifically with the viral hemagglutinin protein (lane 6). Lanes 7 and 8 are MAb 2A-54-5 and 3-60-5, indicating recognition of the same polypeptide. MAb 37-5-1B did not bind to measles virus polypeptides (data not shown).

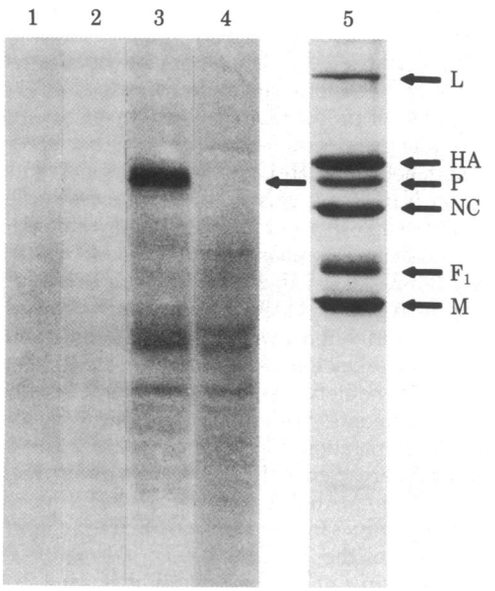

FIG. 3. Immunoblots of reaction of measles virus phosphoprotein with MAb 2A-54-5. Lanes: 1, infected cell cytosol transferred to nitrocellulose paper incubated with labeled second antibody only; 2, the same infected cell cytosol preparation on nitrocellulose paper incubated with P3 cell supernatant fluid and then with a labeled second antibody; 3 and 4, infected cell cytosol and uninfected cell cytosol, respectively, on nitrocellulose paper incubated with MAb 2A-54-5 and with the labeled second antibody; 5, marker purified measles virus labeled with [^{35}S]-methionine. L, RNA polymerase; HA, hemagglutinin; P, phosphoprotein; NC, nucleocapsid; F_1, fusion protein; M, membrane protein.

DISCUSSION

In attempting to produce MAbs to measles virus and HSV-1, we obtained stable clones that secreted antibody reactive both with intermediate filaments of normal cells and with the proteins of measles virus and HSV-1. The M_r 52,000 intermediate filament protein is obtained as insoluble material from cells treated with high-salt/Triton X-100 buffers and is probably vimentin (12). Our staining patterns with 2A-54-5 are similar to those presented by Franke *et al.* (14), who described the rearrangement of cytokeratins and vimentin during the cell cycle. The crossreaction of the intermediate filament protein with the phosphoprotein of measles virus or the protein of HSV was detected by using immunofluorescence and immunoblotting. The 2A-54-5 MAb reacted with the phosphoprotein of measles virus both from infected cells and from purified virus. Similarly, the 37-5-1B MAb reacted with the late protein of HSV-1 both from infected cells and from purified virus (7). Interestingly, the anti-measles virus and anti-HSV MAbs that appear to react with the same or similar intermediate filament proteins react with two different proteins from the respective virus preparations: a M_r 70,000 phosphoprotein from measles virus and a M_r 146,000 ICP6 protein from HSV-1, which is also phosphorylated (15). By immunoblot analysis, HSV-1 MAb (37-5-1B) did not react with measles virus phosphoprotein, suggesting that the MAb to HSV-1 phosphorylated protein and MAb to measles virus phosphoprotein recognize different determinants on intermediate filaments.

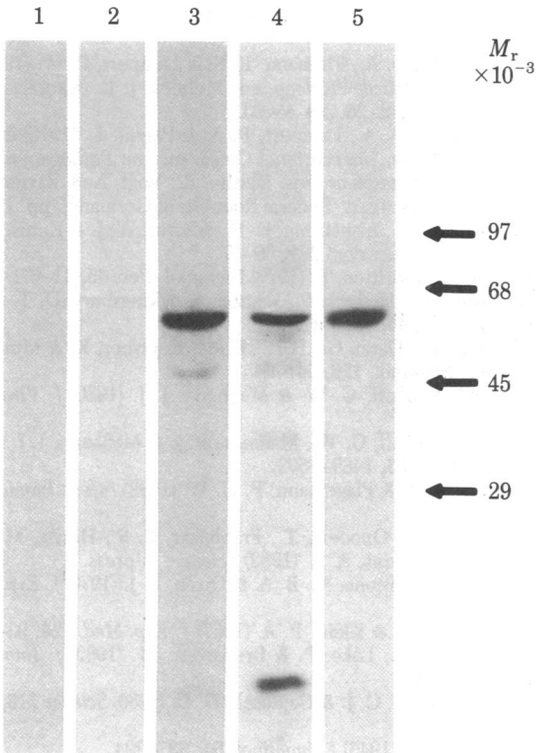

FIG. 4. Immunoblots showing reaction of MAbs to intermediate filaments of HeLa cells. Lanes 1–4 represent nitrocellulose strips to which Triton-insoluble proteins were bound (intermediate filaments); the strips were incubated with various MAbs followed by second labeled antibody. Lanes: 1, P3 supernatant fluid was incubated with the strip, followed by labeled second antibody; 2, a strip incubated with MAb specific for measles virus phosphoprotein (3-60-5); 3, a strip incubated with MAb to intermediate filaments (3-3-2); 4, a nitrocellulose strip incubated with MAb 2A-54-5; 5, strip incubated with MAb 37-5-1B. The prominent band is M_r 52,000 protein.

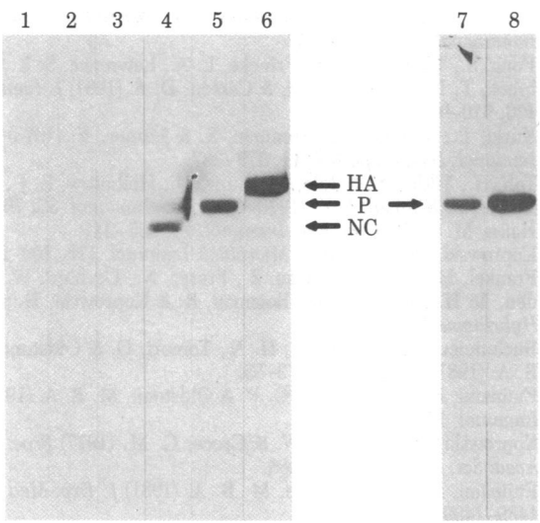

FIG. 5. Immunoblots showing reaction of MAbs with purified measles virus. Lanes 1–8 are nitrocellulose strips to which purified measles virus proteins are bound. Lane 1, reaction with the second antibody alone (affinity-purified ^{125}I-labeled goat anti-mouse Ig); the remaining strips were incubated with various MAbs and then the second antibody. Lanes: 2, reaction with P3 supernatants; 3, MAb to intermediate filaments (3-3-2); 4, measles virus nucleocapsid (NC) MAb; 5, MAb 2A-54-5; 6, MAb to measles virus hemagglutinin (HA); 7 and 8, MAb 2A-54-5 and MAb to phosphoprotein (P), respectively.

There are two alternative explanations for the observed antigenic relationship between vimentin and viral proteins. First, vimentin may have certain sequences (or surface configurations) of amino acids in common with the measles virus phosphoprotein and ICP6 of HSV-1. This relationship may be entirely fortuitous. Alternatively, parts of vimentin itself or vimentin-related intermediate filament proteins may become incorporated into viral proteins in the course of virus replication. This latter explanation would be less trivial than the former because it would lead in a predictable manner to the generation of antibodies crossreacting with viral and intermediate filament proteins. The observations of Blase *et al.* (16) and Dulbecco *et al.* (17) on crossreactive determinants between vimentin and tropomyosin (16), as well as vimentin and Thy-1 antigen (17) and of Pruss *et al.* (12) of common antigenic determinant shared by all classes of intermediate filaments support such mechanisms. This notion of "molecular mimicry" discussed by Lane and Koprowski (18) has several important biological implications. Recently, Wood *et al.* (19) described an antibody that reacts with neurons, cardiac muscle cells, and *Trypanosoma cruzi*. Those investigators suggested that a common antigen seen by this antibody may be important in pathogenic events underlying trypanosomiasis. A similar scenario may occur with viruses that share epitopes with cellular proteins. In this instance, an immune response against virus may result in formation of crossreacting antibodies that bind to "normal" cell surface determinants and result in the modulation of cellular function (20, 21) or lysis of the cell with the cooperation of complement or lymphocytes bearing an Fc fragment receptor. The reaction of autoantibody with intracellular components might yield secondary pathogenic sequelae to viral infection. Cells lysed by virus infection or immune attack expose intracellular determinants. Hence the reaction of autoantibody with self molecules may increase injury at the site of viral infection through the action of complement and other products of inflammation or at distant sites due to trapped immune complexes (22).

On the level of the whole organism, autoimmunity associated with virus infection could occur by several mechanisms in addition to "molecular mimicry." Viruses may act as polyclonal B cell activators (23–29), thereby expanding a preexisting clone that reacts with "self." Viruses may also release antigens not ordinarily recognized by the host immune system. Such events are suggested by experiments with reovirus by Haspel *et al.* (30). Viruses may also alter cellular DNA sufficiently to allow the formation of anti-DNA antibodies (31). Similarly, viruses can potentiate or augment the response to many antigens (32, 33). Any of these mechanisms may explain the appearance of autoantibodies during and after virus infections (1–5, 34) and perhaps the origin of many so-called "natural" antibodies (35–37).

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