Immunol Res 1989;8:3–15

Molecular Mimicry as a Mechanism for Virus-Induced Autoimmunity

Robert S. Fujinami[a], *Michael B.A. Oldstone*[b]

[a] Department of Pathology, University of California, San Diego, La Jolla, Calif., and
[b] Department of Immunology, Research Institute of Scripps Clinic, La Jolla, Calif., USA

Introduction

One of the major questions in biology is, what are the initiating or inciting factors involved in immune responses to self that lead to autoimmune disease? The answer would point to the mechanisms and underlying causes of many chronic diseases such as: rheumatoid arthritis, systemic lupus erythematosus, diabetes, autoimmune kidney and thyroid disease, cardiovascular disease and multiple sclerosis. The underlying cause(s) in many of these diseases is still not understood. Epidemiologic data tend to suggest that viruses and/or other microorganisms in association with immunologic parameters are often linked with episodes of disease.

Among the proposed instigators of autoimmune events is polyclonal B-cell activation by viruses and other microorganisms [reviewed in 1]. Microorganisms produce substances that can directly activate B cells by interacting with their surface receptors. Many such substances including lipopolysaccharide, dextran sulfate, and tuberculin are located in bacterial cell walls. These polyclonal B-cell activators are generally high molecular weight polymers containing repeated determinants, although with an avalanche of cloning and sequence data now available, it has become increasingly clear that many microbial agents also possess proteins with repetitive sequences. Once activated, B cells then proceed to proliferate, differentiate into plasma cells and secrete antibody [2]. This type of stimulation is not immunologically specific but is global in nature.

Viruses that are known polyclonal B-cell activators include Epstein-Barr virus, influenza virus, herpes simplex virus, vesicular stomatitis virus, adenovirus, African swine fever virus, and Sindbis virus [reviewed in 1]. In most instances of infection by these viruses, B cells are driven to differentiate into plasma cells. Autoimmunity could result by stimulation of antiself B lymphocytes. These B cells having receptors of a preprogrammed specificity, including self, have been found in normal individuals [3–5]. Many of these antiself B cells possess the Leu-1$^+$ phenotype [4, 5]. The antibodies to self could be sufficient to cause or promote autoimmune disease when directed against critical cellular sites to which activated complement then binds or through immune complex formation and subsequent accumulation [6].

Viruses may additionally mediate polyclonal B-cell activation through down-regulation of suppressor T-cell populations or augmentation of virus-specific helper T or B cells [1, 7]. Infection of T cells by virus could even alter immune responses to other antigens. Further, autoimmunity may result from virus infection of a subset of T cells that regulates the immune response. Without such regulation, a chronic response to self could occur without the normally functioning checks and balances of the immune system.

Idiotypes and anti-idiotypes may also play a role in autoimmunity [8–11; reviewed in 12, 13]. In the simplest terms, when a virus (antigen) infects a host, a particular antibody (Ab_1) is produced. Ab_1 could be specifically reactive against a site where the virus binds to cells, i.e., neutralizing epitopes. The Ab_1 then elicits an anti-idiotype response (Ab_2). The anti-viral idiotype Ab_2 resembles the viral structure used to bind to cells. Thus, this Ab_2 can bind to similar sites on cell surfaces as virus, but the antibody could modulate cellular function or activate the complement cascade leading to cell injury.

An old concept to account for autoimmunity is the existence of immunologic cross-reactions, or molecular mimicry, i.e., shared determinants between an exogenous agent and self or autoantigen [reviewed in 14, 15]. Recently, technologies have become available [15, 16] to study immunologic cross-reactions at the level of discrete epitopes, alter these epitopes and rapidly compare them with those of other host and/or microbial proteins. Microorganisms can have antigenic determinants in common with the host they infect. In this situation, an immune response against the cross-reacting determinant is also against the shared self structure. The outcome is initiation of disease. These types of cross-reacting immune responses leading to disease are the focus of this report.

Association of Virus and Self

The first suggestive evidence that viruses could share determinants with their hosts came from experiments demonstrating a temporal association between infection and the occurrence of autoantibodies. Ajdukiewicz et al. [17] reported the presence of anti-smooth muscle antibodies in patients with infectious active hepatitis. Later Toh et al. [18] tested 113 sera from children with infectious hepatitis, chickenpox, measles and mumps viruses for reactivity to cytoplasmic intermediate filaments. Sixty-five percent of these sera from infected individuals reacted with the intermediate filament proteins according to immunofluorescent staining. Only 6% of control sera were positive in a similar fashion. Similar antibodies were also found in 81% of 126 patients with infectious mononucleosis [19]. Linder et al. [20] described the presence of autoantibodies to intermediate filament proteins in sera of patients with infectious mononucleosis. Additional studies have documented, other types of autoantibodies in similarly infected patients [21–23]. However, in many of these instances it was not clear whether these antibodies bound to cross-reacting elements between virus and self, or whether the antibodies arose by polyclonal B-cell activation, or both.

After using similar techniques, Sotelo et al. [24] described autoantibodies against axonal neurofilaments in patients with subacute spongiform encephalopathies such as

kuru and Jakob-Creutzfeldt disease. These sera were tested in tissue cultures of central nervous system neurons from several species of rodents. Almost 60% of patients with Jakob-Creutzfeldt disease and 27% of patients with kuru had autoantibodies that bound to neurofilaments. This was the first evidence of an immune reaction occurring in relationship to either of these encephalopathic diseases.

Other factors also influence virus-host interactions that lead to autoimmunity, as experiments in animal models bear out. Kay [25] reported that Sendai virus (parainfluenza type 1) increased autoimmune disease in aged mice and suggested that a decline in T-cell function and virus infection were the contributing events. Thus, T-cell dysregulation and virus infections lead to the production of autoantibodies and the occurrence of autoimmune disease.

In studies of vaccinia virus-infected mice, Steck et al. [26] found that intracerebral inoculation with a neurotropic strain of vaccinia virus resulted in the production of myelin and oligodendrocyte antibodies in serum. No antibodies to neurons or thymocytes were detected. Mice injected with a dermotropic strain of vaccinia did not produce the autoantibodies to myelin or oligodendrocytes. In these studies, neither the antimyelin nor the antioligodendrocyte antibodies were absorbed out by whole vaccinia virus. However, not all vaccinia proteins are expressed in the virion. Thus, the presence of cross-reacting determinants shared by virus and myelin could not be confirmed by the method used. In contrast, Dales et al. [27] demonstrated that immunization of mice with vaccinia virus yielded autoantibodies, particularly to intermediate filament proteins. One of these intermediate filament proteins, vimentin, cross-reacted with vaccinia hemagglutinin (discussed later). These autoantibodies formed whether the mice were immunized with live or UV-inactivated virus. Under the conditions used, viral replication was not necessary for the production of autoantibodies.

In another animal model, Webb et al. [28] and Webb and Fazakerley [29] described a system in which infection of mice with Semliki Forest virus induced antibodies to galactocerebroside, glucocerebroside, total ganglioside and G_{T1b} ganglioside but not against myelin or sulfatide. Injecting the virus peripherally into Swiss mice caused the demyelinating disease, but brain-derived or brain-passaged Semliki Forest virus was needed for the production of autoantibody. The authors predicted that, since Semliki Forest virus has a membrane, it can incorporate part of the host lipid (myelin glycolipids) into that membrane, and it is these components to which an immune response is directed.

Besides autoantibodies arising during virus infections, autoreactive T cells have been observed. Infection of BALB/c mice with a heart-adapted variant of coxsackievirus, group B, type 3, led to the development of myocarditis [30]. T cells isolated from these infected mice were cytolytic to primary cultures of infected and uninfected mouse myocytes. Two populations of T cells could be identified, one that lysed uninfected and another that lysed virus-infected myocytes. It is interesting that both populations of T cells, when injected separately into naive recipients, could induce myocarditis. Antibodies to cardiac tissue were found in the infected mice (neurotropic strain of virus). However, these antibodies appeared not to play a major role in the pathogenesis of the

disease [31]. In contrast, in a different mouse model [32] the presence of heart-specific autoantibodies following infection did correspond with the development of disease.

Recently, suggestions have been made that antibodies to lymphocytes and/or their products can modulate the disease process. In patients with acquired immune deficiency syndrome (AIDS), autoantibodies have been found in association with infection by the human immunodeficiency virus (HIV). Several groups have reported the presence of anti-lymphocyte or lymphocytotoxic antibodies in patients with AIDS. Kloster et al. [33] suggested that these autoantibodies may participate in the immunodeficiency that characterizes AIDS patients. Dorsett et al. [34] found that incubation of normal (uninfected) lymphocytes with sera from patients diagnosed as having AIDS, or AIDS-related complex resulted in increased numbers of surface immunoglobulin-positive lymphocytes. No such increase occurred when lymphocytes from normal individuals were incubated with sera from patients with diseases unrelated to AIDS or from normal control subjects. In dual-labeling studies, these investigators [34] showed that the cells which bound the antibodies were of the OKT-4 or OKT-11 and not OKT-8 phenotype. Therefore, cells of the helper-suppressor phenotype bound the antilymphocyte antibodies, and modulation of the OKT-4 cell may be involved in the pathogenesis of AIDS.

Direct Evidence for Cross-Reactivity

Direct evidence that microorganisms and/or share antigenic sites or determinants with self components initially came from data generated in studies involving bacteria. Shorb and Bailey [35] tested 187 strains from 81 bacterial species and found that 15 of these species contained Forssman antigen, a natural component of human serum. The presence of this antigen could not be attributed to a contaminant within the growth medium, since the bacteria were grown in medium lacking the Forssman antigen. Later, Springer et al. [36] examined 282 strains of gram-negative bacteria and found that approximately half of the strains had A, B, and O blood group activity. In addition, during this period of time Springer and Tritel [37] demonstrated that semipurified influenza virus contained blood group-A antigen; however, direct analysis was difficult. There is strong evidence for determinants common to HLA B27 and Klebsiella has been reported [38, 39]. Cross-reactions and a relationship between streptococci and self also have been eloquently described. These have been reviewed by Zabriskie et al. [40, 42] and Read and Zabriskie [41] and are not discussed here.

Mounting evidence that viruses share antigenic sites or determinants with self components was confirmed with the development of monoclonal antibody technology. This technique allowed the production of large amounts of antibody with one unique specificity. Before monoclonals were available, antibodies to self components were often detected in the circulations of virus-infected individuals (previous section); however, there was no easy way to determine whether these antibodies arose through molecular mimicry, i.e. common epitopes. Now by using monoclonal antibodies, common sites on viral proteins and host cell proteins can be substantiated.

Lane and Hoeffler [43] described a monoclonal antibody that reacted with the SV40 T

antigen and with a host cell protein of molecular weight 68,000. Harlow et al. [44] and Crawford et al. [45] extended these findings by showing the binding of several monoclonal antibodies to SV40 T antigens and to a variety of host cell proteins ranging in molecular weights from 35,000 to 150,000. These authors suggested that the sites shared by the viral T and host proteins reflect similarities of function and shape. These common sites may be involved in gene regulation since many of the host proteins in question appear to be nuclear.

Fujinami et al. [46] described cross-reactions between virus and self, i.e., molecular mimicry, in the context of autoimmunity and used monoclonal antibodies as tools to probe the common sites. One of the measles virus proteins, phosphoprotein, was shown to have a site in common with a cytokeratin protein of normal cells. This was demonstrated first by immunofluorescent staining of measles virus infected and uninfected cells, and second by Western blotting analysis. Both methods concurred in that the monoclonal antibody reacted with the 70,000 molecular weight measles virus phosphoprotein and one of the cytokeratin proteins (54,000 molecular weight) from normal cells. Thus, this indicates that there is a common antigenic site between a viral protein and a normal host cell protein. Monoclonal antibodies have identified similar reactivities in many viral systems. Recently, Srinivasappa et al. [47] reported that roughly 3–4% of all antiviral monoclonal antibodies react with host cells components.

In addition, Fujinami et al. [46] demonstrated a cross-reaction between an intermediate filament protein and a herpes virus protein of 146,000 molecular weight. The monoclonal antibody bound to and immunoprecipitated this protein during the late phase of herpes virus infection. As mentioned, Dales et al. [27] also found a cross-reacting epitope between vaccinia virus hemagglutinin and vimentin, another intermediate filament protein, thus showing common antigenic determinants between virus and self. It is interesting that many of the monoclonal antibodies cross-react with intracellular determinants or filaments. This probably reflects the fact that viruses are intracellular parasites and assemble in very discrete sites within the infected cell [48]. These regions common to both virus and intermediate filament proteins would facilitate transport of the virus and intermediate filament to the same compartments occupied by intermediate filament proteins and allow viral assembly.

In support of cross-reacting determinants shared by human retrovirus and host, Haynes et al. [49] reported that a monoclonal antibody reacted against a 19,000-dalton HIV protein and a neuroendocrine component of human thymic epithelial cells. This determinant was not found on other normal epithelial or neuroendocrine tissues of humans. The antigen first appeared in the thymus at between 8 and 15 weeks of gestation and was present in the subcapsular cortical and medullary thymic epithelium by 3 years of age. Other studies by Sarin et al. [50] demonstrated that antiserum to thymosin alpha-1 could neutralize human T-cell leukemia virus (HTLV)-III/LAV. The reverse transcriptase activity and expression of the p15 and p24 viral proteins were inhibited by purified immunoglobulin preparations from antisera to thymosin alpha-1. These authors suggested that the common epitope(s) between virus and host could explain the lack

of effective neutralizing antibodies in patients with AIDS. A close resemblance between the viral determinant and one belonging to the host could prevent the latter from eliminating the virus so that viremia would persist. In contrast, antibodies that do develop may initiate autoimmune processes that lead to damage or destruction of the epithelial hormone-producing cells of the thymus. The authors suggested that this may be why, in many individuals infected with HIV, the thymus glands are significantly smaller than normal, and severe epithelial destruction has been observed in infected patients. However, the rabbits used to prepare the antithymosin alpha-1 antibody did not undergo thymus gland destruction even though high titers of antibodies were present, and the animals were observed for up to 2 years.

A cross-reacting determinant has also been described between murine mammary tumor virus and a subpopulation of B cells [51]. A monoclonal antibody VE7 detects the gp52 envelope glycoprotein of murine mammary tumor virus. In addition, the VE7 reacts with 2.5–4.5% of splenic lymphocytes and a subpopulation of cells that are Thy1.2-negative, surface immunoglobulin-positive. These cells are small lymphocytes rather than plasma cells and are not restricted to one particular immunoglobulin class. Further the B-cell determinant does not appear to be a differentiation antigen.

Sheshberadaran and Norrby [52] described monoclonal antibodies against measles virus fusion protein that cross-react with a host cellular stress protein of 79,000 molecular weight. This was demonstrated by immunoprecipitation and immunofluorescent staining of infected and uninfected cells. This host stress protein is induced by infection of cells with various paramyxoviruses, heat shock of uninfected HeLa cells, and treatment of various cell lines with 2-deoxyglucose, tunicamycin, or *L*-canavanine.

In producing monoclonal antibodies to another paramyxovirus, Goswami et al. [53] found that an antibody against the Simian virus 5 HN glycoprotein reacts with an antigen found in Purkinje cells of the adult rat brain. This monoclonal antibody has the ability to neutralize the virus. In addition, upon treatment of brain sections with acetic acid-ethanol, this monoclonal antibody binds to myelin-containing areas. This antibody is also positive in reactivity to human brain sections or tissue extracts as tested by immunohistochemical staining, ELISA and radioimmunoassays.

A monoclonal antibody against Theiler's virus has been described as reactive with galactocerebroside [54]. This virus has the ability to cause a chronic demyelinating disease in mice. The cross-reacting monoclonal antibody neutralizes the virus and, when injected into the rat siatic nerve can cause demyelination in vivo. The presence of such an antibody could contribute to the observed pattern of this disease.

Recently, Sairenji et al. [55] described a murine monoclonal antibody that recognized a filamentous structure in Epstein-Barr virus-producing lymphoblastoid cell lines. By immunofluorescent staining, the monoclonal antibody appeared to react with vimentin or a closely associated intermediate filament protein. The expression of this antigen was induced by superinfection with Epstein-Barr virus or treatment with tumor promoting agents, and its appearance may be similar to the induction of stress proteins [52].

Tardieu et al. [56] have found shared antigenicity between reovirus types 1 and 3 and lymphocytes. The monoclonal antibody they tested reacts with the Lyt 2,3 subset of murine lymphocytes as demonstrated by indirect immunofluorescent staining. Further, this monoclonal antibody has the ability to mediate complement-dependent lysis of Lyt 2,3 cells.

Direct Comparisons of Amino Acid Sequences

Monoclonal antibodies are excellent reagents to use in describing antigenic sites common to virus and host; however, this method does not readily allow the identification of the specific region on the shared proteins or determinants. To approach this problem directly, peptide stretches of known disease-producing areas from host proteins can be determined. These amino acid sequences, by themselves, should cause autoimmune disease when injected with adjuvant into a suitable animal. The disease-producing sequences, once analyzed, are the basis of computer searches for viral proteins bearing regions of homology to them.

This approach has been used successfully by Fujinami and Oldstone [57; reviewed in 16]. One of the homologies found is a region from myelin basic protein (amino acid 66–75) and the hepatitis B virus polymerase (amino acid 589–598) [57]. The amino acid stretch from this region of myelin basic protein is encephalitogenic for the rabbit. That is, these amino acids injected with adjuvant into a rabbit will routinely induce an autoimmune disease known as experimental allergic encephalitis (EAE). By computer analysis, hepatitis B virus polymerase was found to share six amino acids in tandom with the encephalitogenic region for the rabbit.

The relevant viral polymerase region was synthesized, and the resulting viral peptide was then injected with Freund's complete adjuvant into rabbits. The animals were monitored for autoantibody production (antibody to myelin basic protein), cellular reactivity to myelin basic protein and disease production [57]. When the sera from 7 rabbits immunized with one injection of viral peptide were tested for antibody to myelin basic protein, 5 had significant levels of antibody. The binding of this antibody to myelin basic protein could be inhibited by the viral peptide, demonstrating specificity. Therefore, sensitization of a rabbit using a viral peptide that cross-reacts with a self protein can lead to autoantibody production.

To test for cellular reactivity, peripheral blood lymphocytes from 8 rabbits sensitized with the viral peptide, were tested for their ability to respond to myelin basic protein or viral peptide. Peripheral blood lymphocytes from all the sensitized rabbits proliferated when cultured with the viral peptide, indicating a positive reaction. Subsequently, peripheral blood lymphocytes from 4 of the 8 rabbits responded positively to myelin basic protein, the self component.

The brains and spinal cords of 11 rabbits sensitized with the viral peptide were examined for histologic lesions characteristic of EAE. Four of these animals developed cellular infiltrates, and lesions in the central nervous system that were consistent with the histologic changes observed in this autoimmune disease.

As more sequence information is generated, additional comparisons can be made between proteins from microorganisms and

receptive hosts. Kagnoff et al. [58] described an amino acid homology between A-gliadin, a component of wheat, and a 54,000 molecular weight early region E1b protein of human adenovirus type 12. This virus can usually be isolated from the human intestinal tract. The homologous region includes a 12 amino acid stretch where 8 residues are in common, 5 of which are in tandom. Both regions are hydrophilic according to computer prediction. Antibodies to the adenovirus 12 region cross-react with A-gliadin. Celiac disease in humans is activated by ingestion of grains containing gliadins or similar proteins. Thus, these authors suggest that, if the common site is important in disease production, then an immune response against a normal intestinal parasite, such as adenovirus type 12, could result in manifestations similar to those caused by ingestion of gliadins. However, genetic factors also contribute to the expression of celiac disease.

Similarly, Clarke et al. [59] describe a homology between the HTLV envelope (env) gene and HLA class-I gene. By using molecular clones of HTLV and the human MHC antigen DNA, a region of homology was found in the env region of HTLV and a region in the HLA-B locus that encodes the extracellular portion of class-I molecules. These authors suggest that viral binding to cells which recognize the homologous HLA antigen would be enhanced. In addition, these authors speculate that T cells expressing the inappropriate HLA antigen would be impaired in their normal functions. Further, the viral HLA-related antigen that appears as self might evade cellular responses that would occur if this antigen were recognized as foreign. Along this line, Reither et al. [60] described a region of homology between the env protein of HIV and a portion of interleukin 2 that purportedly binds to the IL-2 receptor. This homology suggests a possible mechanism for the characteristic immunosuppression often observed in AIDS patients. The AIDS virus env protein could interfere with IL-2 activity either by competing with IL-2 for the receptor or after binding to the cell. This phenomenon was also apparent for the env proteins of other retroviruses associated with immunosuppression. Weigent et al. [61] demonstrated that a peptide from the carboxy terminus of the HIV env protein inhibited the biologic activity of human IL-2 in a murine spleen cell proliferation assay. When the peptide was conjugated to a protein carrier, the peptide-carrier inhibited the binding of radiolabeled IL-2 to its receptor. Besides binding to the receptor and competing with IL-2, autoantibody to this site would effectively bind to the IL-2 receptor and could inhibit the of action of IL-2.

In work with other retroviruses, Wong and Goldberg [62] produced antibodies to a decapeptide from pp60 src of Rous sarcoma virus (RSV). The peptide inhibited the kinase activities associated with the transforming proteins of pp60 src, P90 of Y73 avian sarcoma virus or P140 of Fujinami sarcoma virus. The antiserum to this peptide could immunoprecipitate the pp60 src of RSV and P90 of the Y73 avian sarcoma virus. This antiserum could also precipitate a number of high molecular weight phosphoproteins from normal chicken and rat fibroblasts and from several lines of virus-transformed cells, indicating a cross-reacting epitope with the host. Mathey-Prevot et al. [63] obtained an antiserum specific for the unique sequence of the transforming protein p140 of Fujinami sarcoma virus that is capable of immunoprecipitating a normal cellular protein of 98,000 molecular weight. The cellular pro-

tein is structurally similar to the viral p140 as shown by tryptic peptide mapping, and both the viral and cellular proteins have identical protein kinase activity. From sequence studies, Robbins et al. [64] described similarities between the simian sarcoma virus-transforming gene product p28 and human platelet-derived growth factor (PDGF). Post-translational processing of the transforming gene produce yields an 11,000 and 20,000 molecular weight polypeptide. It is the larger polypeptide that is similar to an 18,000 molecular weight form of the human PDGF. Antisera to human PDGF recognizes the viral-transforming polypeptide. These similarities may relate to the process by which the transforming protein could operate.

Ito et al. [65] raised antibodies to an amino acid sequence in the middle T antigen of polyoma virus. The sequence is thought to be important in transformation. The antiserum reacts with a cellular protein of 130,000 from mouse and rat cells and middle T antigen, a reaction that is blocked by the addition of peptide. By immunofluorescence, this antibody stains uninfected mouse, rat, human and chicken cell microfilaments. This pattern of staining and distribution of label are similar to that observed with anti-actin antibodies. The 130,000 protein migrates slower than vinculin and faster than myosin light chain kinase.

The adenovirus glycoprotein (19,000 molecular weight) is encoded by the E3 region of the virus genome. This protein is expressed on the cell membrane and presumably binds to HLA class-I antigen. Chatterjee and Maizel [66] found that the adeno protein resembles the HLA class-II antigen in domain structure and amino acid sequence. The alpha chain of the class-II antigen domain nearest the cell membrane and intramembrane region resemble the adenovirus protein. This region has similar regions in common with the several HLA proteins and microglobulin. Recently, Fujinami et al. [67] used computer analysis to find a sequence homology and immunologic cross-reactivity between human cytomegalovirus and the HLA-DR beta chain. The sequence homology is encoded by the IE-2 region of human cytomegalovirus and a conserved domain of HLA-DR. The shared region has similar hydrophilicity and predicted beta turn potential. Antiserum to the viral peptide binds to the HLA beta chain and this binding is inhibited by the peptide. This type of mechanism could explain how cytomegalovirus infection contributes to graft rejection following transplantation.

Lentz et al. [68] found similarly comparable regions in the sequence of rabies glycoprotein and that of snake venom curaremimetic neurotoxins, potent ligands of the acetylcholine receptor. The greatest similarity occurred with residues important in neurotoxicity including those interacting with the acetylcholine-binding site of the acetylcholine receptor. This region of the viral glycoprotein may function as a recognition site for the acetylcholine receptor. Direct binding of the rabies virus glycoprotein to the acetylcholine receptor could contribute to the neurotropism of this virus. Similarly, Nemerow et al. [69] show sequence homology between the gp350 of Epstein-Barr virus and the complement fragment C3d. A computer comparison of the deduced gp350 amino acid sequence with that of human C3d reveals two regions of primary sequence homology. This finding suggests that a common region on these two unrelated proteins may be involved in Epstein-Barr virus binding to the CR2 receptor of human B cells.

Blomquist et al. [70] have described a relationship between a 19,000 vaccinia virus protein and two growth factors. The similarity is at the level of conserved cysteine and glycine residues. Epidermal growth factor and transforming growth factor type 1 as well as several of the clotting factors have a pattern of cysteine and glycines identical to that of the 19,000 molecular weight vaccinia virus protein. These authors suggest that the two proteins may have originated from the same progenitor molecule.

Walker and Jeffrey [71] found regions of *Escherichia coli* histidyl-tRNA synthetase and alanyl-tRNA synthetase that bear homology to several viral and muscle proteins. The two synthetase proteins were recently identified as autoantigens in polymyositis. The authors predict that molecular mimicry and a viral etiology are involved in the development of polymyositis.

Similarly, many investigators [57, 72–74] have looked for homologies between central nervous system proteins and microorganisms. All have suggested that immunologic cross-reactions between virus and myelin could be involved in the pathogenesis of post-infectious encephalopathies or multiple sclerosis.

These types of experiments provide clues to link molecular mimicry and autoimmune disease. Infection by a virus can lead to an antiviral immune response. Should this response be against a determinant on the virus that is similar or identical to a site on a host protein, tissue- or cell-specific injury could result. The responsible mechanism for injury would be the generation of cytotoxic cells specific for cross-reacting sites or the production of antibody. This antibody would bind to the common site, the complement cascade would unfold and result in cellular destruction. In addition, immune complex deposition would initiate disease in the kidneys, arteries and/or choroid plexes.

Once the cross-reacting immune response is set in motion, the initiating agent need not be present. The virus may be cleared or eliminated from the body, yet the humoral or cellular elements continue to attack self components resulting in injury. As the injured tissue releases more self antigen, the cycle of destruction continues. In this situation, the probability of virus being recovered from the actual sites of damage is unlikely.

Autoimmune disease probably occurs only when the actual site shared between virus and host is amenable to disease induction. In the earlier example of homology between the encephalitogenic (disease inducing) site and viral polymerase, actual disease would not occur if the host site did not take part in the disease. Should the cross-reaction take place at a site not involved in disease production, autoantibody may form but no tissue damage would follow. An example of autoimmune disease within the central nervous system may be what is sometimes observed in patients with measles virus infection. This virus can cause a post-infectious encephalopathy on rare occasions, perhaps as exemplified experimentally when peripheral blood mononuclear cells from such patients proliferate in cultures containing myelin basic protein [75]. Measles virus proteins may share common elements with myelin basic protein or other central nervous system proteins. This remains to be determined. Similar sets of events could play a role in Guillain-Barré syndrome, myasthenia gravis, thyroiditis, arthritis, diabetes and multiple sclerosis in which immunologic events play a pivotal role.

Acknowledgments

This work was supported by National Multiple Sclerosis Society and the National Institutes of Health. We thank Mrs. Diana Ferris for her excellent help in manuscript preparation.

References

1 Ahmed, R.; Oldstone, M.B.A.: Mechanisms and biological implications of virus induced polyclonal B-cell activation; in Notkins, Oldstone, Concepts in viral pathogenesis, pp. 231–238 (Springer, New York 1984).
2 Coons, A.H.; Leduc, E.H.; Connolly, J.M.: Study on antibody production. I. A method for the histological demonstration of specific antibody and its application to a study of the hyperimmune rabbit. J. exp. Med. *102:* 49–60 (1955).
3 Casali, P.; Inghirami, G.; Nakamura, M.; Davis, T.F.; Notkins, A.L.: Human monoclonals from antigen-specific selection of B lymphocytes and transformation by EBV. Science *234:* 476–479 (1986).
4 Casali, P.; Burastero, S.E.; Makamura, M.; Inghirami, G.; Notkins, A.L.: Human lymphocytes making rheumatoid factor and antibody to DNA belonging to LEU-1$^+$ B-cell subset. Science *236:* 77–81 (1987).
5 Hardy, R.R.; Hayakawa, K.; Shimizu, M.; Yamasaki, K.; Kishimoto, T.: Rheumatoid factor secretion from human Leu-1$^+$ B cells. Science *236:* 81–83 (1987).
6 Oldstone, M.B.A.; Lampert, P.A.; Perrin, L.: Formation of virus-antiviral antibody immune complexes; in Kluthe, Vogt, Batsford, International Conference on Pathogenesis, Pathology and Treatment, 1976. Glomerulonephritis, pp. 12–19 (Thieme, Stuttgart 1976).
7 Mims, C.A.: The pathogenesis of infectious disease (Academic Press, London 1982).
8 Sege, K.; Peterson, P.A.: Use of anti-idiotypic antibodies as cell-surface receptor probes. Proc. natn. Acad. Sci. USA *75:* 2443–2447 (1978).
9 Wassermann, N.H.; Penn, A.S.; Freimuth, P.I.; Treptow, N.; Wentzel, S.; Cleveland, W.L.; Erlanger, B.F.: Anti-idiotypic route to anti-acetylcholine receptor antibodies and experimental myasthenia gravis. Proc. natn. Acad. Sci. USA *79:* 4810–4814 (1982).
10 Zanetti, M.; Rogers, J.; Katz, D.H.: Induction of autoantibodies to thyroglobulin by anti-idiotypic antibodies. J. Immun. *133:* 240–243 (1984).
11 Essani, K.; Satoh, J.; Prabhakar, B.S.; McClintock, P.R.; Notkins, A.L.: Anti-idiotypic antibodies against a human multiple organ-reactive autoantibody. J. clin. Invest. *76:* 1649–1656 (1985).
12 Kennedy, R.C.; Dressman, G.R.: Immunoglobulin idiotypes: Analysis of viral antigenantibody systems. Prog. med. Virol., vol. 31, pp. 168–182 (Karger, Basel 1985).
13 Geha, R.S.: Idiotypic-anti-idiotypic interactions in man. Am. J. Dis. Child. *139:* 417–420 (1985).
14 Damian, R.T.: Molecular mimicry: antigen sharing by parasite and host and its consequences. Am. Nat. *98:* 129–149 (1964).
15 Oldstone, M.B.A.; Schwimmbeck, P.; Dyrberg, T.; Fujinami, R.: Mimicry by virus of host molecules: implications for autoimmune disease. Prog. Immunol. *6:* 787–795 (1986).
16 Dyrberg, T.; Oldstone, M.B.A.: Peptides as probes to study molecular mimicry and virusinduced autoimmunity. Curr. Top. Microbiol. Immunol. *30:* 25–37 (1986).
17 Ajdukiewicz, A.B.; Dudley, F.J.; Fox, R.A.; Doniach, D.; Sherlock, S.: Immunological studies in an epidemic of infective, short incubation hepatitis. Lancet *i:* 803–806 (1972).
18 Toh, H.; Yildie, A.; Sotelo, J.; Osung, O.; Holborow, E.J.; Kanakoudi, F.; Small, J.V.: Viral infectious and IgM autoantibodies to cytoplasmic intermediate filaments. Clin. exp. Immunol. *37:* 76–82 (1979).
19 Holborow, E.J.; Hemsted, E.H.; Mead, S.V.: Smooth muscle autoantibodies in infectious mononucleosis. Br. med. J. *ii:* 323–325 (1973).
20 Linder, E.; Kurki, P.; Andersson, L.C.: Autoantibodies to 'intermediate filaments' in infectious mononucleosis. Clin. Immunol. Immunopathol. *14:* 411–417 (1979).
21 Whitehouse, J.M.A.; Ferguson, N.; Currie, G.A.: Autoantibody to microtubules in infectious mononucleosis. Clin. exp. Immunol. *17:* 227–235 (1974).
22 Sutton, R.N.P.; Edmond, R.T.D.; Thomas, D.B.; Doniach, D.: The occurrence of autoantibodies in infectious mononucleosis. Clin. exp. Immunol. *17:* 427–436 (1974).
23 Anderson, P.; Faber, V.: Antibodies to smooth muscle and other tissue components in infectious mononucleosis. Scand. J. infect. Dis. *20:* 1–5 (1978).
24 Sotelo, J.; Gibbs, C.J.; Gajdusek, D.C.: Autoantibodies against axonal neurofilaments in patients with kuru and Creutzfeldt-Jakob disease. Science *210:* 190–193 (1980).
25 Kay, M.M.B.: Parainfluenza infection of aged mice results in autoimmune disease. Clin. Immunol. Immunopathol. *12:* 301–315 (1979).
26 Steck, A.J.; Tschannen, R.; Schaefer, R.: Induction of antimyelin and antioligodendrocyte antibodies by vaccina virus. An experimental study in the mouse. J. Neuroimmunol. *1:* 117–124 (1981).
27 Dales, S.; Fujinami, R.S.; Oldstone, M.B.A.: Infection with vaccinia favors the selection of hybridomas synthesizing autoantibodies against intermediate filaments, one of them cross-reacting with the virus hemagglutinin. J. Immun. *131:* 1546–1553 (1983).

28 Webb, H.E.; Mehta, S.; Gregson, N.A.; Leibowitz, S.: Immunological reaction of the demyelinating semiliki forest virus with immune serum to glycolipids and its possible importance to central nervous system viral auto-immune disease. Neuropath. appl. Neurobiol. *10:* 77–84 (1984).

29 Webb, H.E.; Fazakerley, J.K.: Can viral envelope glycolipids produce auto-immunity, with reference to the CNS and multiple sclerosis. Neuropath. appl. Neurobiol. *10:* 1–10 (1984).

30 Huber, S.A.; Lodge, P.A.: Coxsackievirus B-3 myocarditis in BALB/c mice: evidence for autoimmunity to myocyte antigens. Am. J. Path. *116:* 21–29 (1984).

31 Huber, S.A.; Lynden, D.C.; Lodge, P.A.: Immunopathogenesis of experimental coxsackie virus induced myocarditis: role of autoimmunity. Herz *10:* 1–7 (1985).

32 Wolfgram, L.J.; Beisel, K.W.; Rose, N.R.: Heart-specific autoantibodies following murine coxsackie-virus B3 myocarditis. J. exp. Med. *161:* 1112–1121 (1985).

33 Kloster, B.E.; Tomar, R.H.; Spira, T.J.: Lymphocytotoxic antibodies in the acquired immune deficiency syndrome (AIDS). Clin. Immunol. Immunopathol. *30:* 330–335 (1984).

34 Dorsett, B.; Cronin, W.; Chuma, J.; Ioachim, H.L.: Anti-lymphocyte antibodies in patients with the acquired immune deficiency syndrome. Am. J. Med. *78:* 621–626 (1985).

35 Shorb, M.S.; Bailey, G.H.: Heterophile antigen in various bacterial species. Am. J. Hyg. *19:* 148–183 (1934).

36 Springer, G.F.; Williamson, P.; Brandes, W.C.: Blood group activity of gram-negative bacteria. J. exp. med. *113:* 1077–1093 (1961).

37 Springer, G.F.; Tritel, H.: Blood group A active substances in embryonated chicken eggs and their relation to egg-grown virus. Science *138:* 687–688 (1962).

38 Welsh, J.; Avakin, H.; Cowling, P.; Ebringer, A.; Wooley, P.; Panayi, G.; Ebringer, R.: Ankylosing spondylitis, HLA B27 and Klebsiella. Cross-reactivity studies with rabbit antisera. Br. J. exp. Path. *61:* 85–91 (1980).

39 Schwimmbeck, P.L.; Yu, D.T.Y.; Oldstone, M.B.A.: Autoantibodies to HLA B27 in the sera of HLA B27 patients with ankylosing spondylitis and Reiter's syndrome: molecular mimicry with *Klebsiella pneumoniae* as potential mechanism of autoimmune disease. J. exp. Med. (in press).

40 Zabriskie, J.B.; Hsu, K.C.: Seegal, B.C.: Heart-reactive antibody associated with rheumatic fever: Characterization and diagnostic significance. Clin. exp. Immunol. *7:* 147–159 (1970).

41 Read, S.E.; Zabriskie, J.B.: Streptococcal diseases and the immune response (Academic Press, New York 1980).

42 Zabriske, J.B.; Engle, M.A.; Villarreal, H.: Clinical immunology of the heart (Wiley, New York 1981).

43 Lane, D.P.; Hoeffler, W.K.: SV40 large T shares an antigenic determinant with a cellular protein of molecular weight 68,000. Nature *288:* 167–170 (1980).

44 Harlow, E.; Crawford, L.V.; Pim, D.C.; Williamson, N.M.: Monoclonal antibodies specific for the SV40 tumor antigens. J. Virol. *39:* 861–869 (1981).

45 Crawford, L.; Leppard, K.; Lane, D.; Harlow, E.: Cellular proteins reactive with monoclonal antibodies directed against simian virus 40 T-antigen. J. Virol. *42:* 612–620 (1982).

46 Fujinami, R.S.; Oldstone, M.B.A.; Wroblewska, Z.; Frankel, M.E.; Koprowski, H.: Molecular mimicry in virus infection: cross-reaction of measles virus phosphoprotein or of herpes simplex virus protein with human intermediate filaments. Proc. natn. Acad. Sci. USA *80:* 2346–2350 (1983).

47 Srinivasappa, J.; Saegusa, J.; Prabhakar, B.S.; Gentry, M.K.; Buchmeier, M.J.; Wiktor, T.J.; Koprowski, H.; Oldstone, M.B.A.; Notkins, A.L.: Molecular mimicry: frequency of reactivity of monoclonal antiviral antibodies with normal tissues. J. Virol. *57:* 397–401 (1986).

48 Casjens, S.: Virus structure and assembly (Jones and Bartlett, Boston 1985).

49 Haynes, B.F.; Robert-Guroff, M.; Metzgar, R.S.; Franchini, G.; Kalyanaraman, V.S.; Palker, T.J.; Gallo, R.C.: Monoclonal antibody against human T cell leukemia virus p19 defines a human thymic epithelial antigen acquired during ontogeny. J. exp. Med. *157:* 907–920 (1983).

50 Sarin, P.S.; Sun, D.K.; Thornton, A.H.; Naylor, P.H.; Goldstein, A.L.: Neutralization of HTLV-III/LAV replication by antiserum to thymosin a. Science *232:* 1135–1137 (1986).

51 Tax, A.; Ewert, D.; Manson, L.A.: An antigen cross-reactive with gp52 of mammary tumor virus is expressed on a B cell subpopulation of mice. J. Immun. *130:* 2368–2371 (1983).

52 Sheshberadaran, H.; Norrby, E.: Three monoclonal antibodies against measles virus F protein cross-react with cellular stress proteins. J. Virol. *52:* 995–999 (1984).

53 Goswami, K.K.A.; Morris, R.J.; Rastogi, S.C.; Lange, L.S.; Russell, W.C.: A neutralizing monoclonal antibody against a paramyxovirus reacts with a brain antigen. J. Neuroimmunol. *9:* 99–108 (1985).

54 Fujinami, R.S.; Powell, H.C.: Monoclonal antibody defines determinant between Theiler's virus and galactocerebroside. J. Neuroimmunol. (in press).

55 Sairenji, T.; Nguyen, Q.V.; Woda, B.; Humphreys, R.E.: Immune response to intermediate filament-associated Epstein-Barr virus-induced early antigen. J. Immun. (in press).

56 Tardieu, M.; Powers, M.L.; Hafler, D.A.; Hauser, S.L.; Weiner, H.L.: Autoimmunity following viral infection: demonstration of monoclonal antibodies against normal tissue following infection of mice with reovirus and demonstration of shared antigenicity between virus and lymphocytes. Eur. J. Immunol. *14:* 561–565 (1984).

57 Fujinami, R.S.; Oldstone, M.B.A.: Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. Science *230:* 1043–1045 (1985).
58 Kagnoff, M.F.; Austin, R.K.; Hubert, J.J.; Bernardin, J.E.; Kasarda, D.D.: Possible role for a human adenovirus in the pathogenesis of celiac disease. J. exp. Med. *160:* 1544–1557 (1984).
59 Clarke, M.F.; Gelmann, E.P.; Reitz, M.S., Jr.: Homology of human T-cell leukaemia virus envelope gene with class I HLA gene. Nature *305:* 60–62 (1983).
60 Reither, W.E.; Blalock, J.E.; Brunck, T.K.: Sequence homology between acquired immunodeficiency syndrome virus envelope protein and interleukin 2. Proc. natn. Acad. Sci. USA *83:* 9188–9192 (1986).
61 Weigent, D.A.; Hoeprich, P.D.; Bost, K.L.; Brunck, T.K.; Reiher, W.E.; Blalock, J.E.: The HTLV-III envelope protein contains a hexapeptide homologous to a region of interleukin-2 that binds to the interleukin-2 receptor. Biochem. Biophys. Res. Commun. *139:* 367–374 (1986).
62 Wong, T.W.; Goldberg, A.R.: Synthetic peptide fragment of src gene product inhibits the src protein kinase and cross reacts immunologically with avian orc kinases and cellular phosphoproteins. Proc. natn. Acad. Sci. USA *78:* 7412–7416 (1981).
63 Mathey-Prevot, B.; Hanafusa, H.; Kawai, S.: A cellular protein is immunologically crossreactive with and functionally homologous to the Fujinami sarcoma virus transforming protein. Cell *28:* 897–906 (1982).
64 Robbins, K.C.; Antoniades, H.N.; Devare, S.G.; Hunkapiller, M.W.; Aaronson, S.A.: Structural and immunological similarities between simian sarcoma virus gene product(s) and human platelet-derived growth factor. Nature *305:* 605–608 (1983).
65 Ito, Y.; Hamagishi, Y.; Segawa, K.; Dalianis T.; Appella, E.; Willingham, M.: Antibodies against a nonapeptide of polyomavirus middle T antigen: cross-reaction with a cellular protein(s). J. Virol. *48:* 709–720 (1983).
66 Chatterjee, D.; Maizel, J.V.: Homology of adenoviral E3 glycoprotein with HLA-DR heavy chain. Proc. natn. Acad. Sci. USA *81:* 6039–6043 (1984).
67 Fujinami, R.S.; Nelson, J.A.; Walker, L.; Oldstone, M.B.A.: Sequence homology and immunologic cross reactivity of human cytomegalovirus with HLA-DR b chain: a means for graft rejection and immunosuppression. J. Virol. (in press).
68 Lentz, T.L.; Wilson, P.T.; Hawrot, E.; Speicher, D.W.: Amino acid sequence similarity between rabies virus glycoprotein and snake venom curaremimetic neurotoxins. Science *226:* 847–848 (1984).
69 Nemerow, G.R.; Mold, C.; Schwend, V.K.; Tollefson, V.; Cooper, M.R.: Identification of gp350 as the viral glycoprotein mediating attachment of Epstein-Barr virus (EBV) to the EBV/C3d receptor of B cells: Sequence homology of gp350 and C3 complement fragment C3d. J. Virol. *61:* 1416–1420 (1987).
70 Blomquist, M.C.; Hunt, L.T.; Barker, W.C.: Vaccinia virus 19-kilodalton protein: relationship to several mammalian proteins, including two growth factors. Proc. natn. Acad. Sci. USA *81:* 7363–7367 (1984).
71 Walker, E.J.; Jeffrey, P.D.: Polymyositis and molecular mimicry, a mechanism of autoimmunity. Lancet *ii:* 605–607 (1986).
72 Jahnke, U.; Fischer, E.H.; Alvord, E.C., Jr.: Sequence homology between certain viral proteins and encephalitogenic and neuritogenic proteins. Science *229:* 282–284 (1985).
73 Shaw, S.-Y.; Laursen, R.A.; Lees, M.B.: Analogous amino acid sequences in myelin proteolipid and viral proteins. FEBS Lett. *207:* 266–270 (1986).
74 Aw, S.E.: Autoimmune disease – pathogenesis through molecular mimicry at the tripeptide level. Ann. Acad. Med. *15:* 546–554 (1986).
75 Johnson, R.T.; Griffin, D.E.; Hirsch, R.L.; Wolinsky, J.S.; Roedenbech, S.; de Soriano, I.L.; Vaisberg, A.: Measles encephalomyelitis – clinical and immunologic studies. New Engl. J. Med. *310:* 137–141 (1984).

Robert S. Fujinami, PhD
Department of Pathology, M-012
University of California, San Diego
La Jolla, CA 92093 (USA)