Immunity to viruses

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Introduction

Viruses are a common cause of infection and may lead to many kinds of disease. Viral clearance is an important factor for the survival of the host, and one of the most important events in clearing a viral infection is the host immune response. Normally, the immune system recognizes a virus as a foreign molecule in the context of major histocompatibility complex (MHC) antigens and mounts an immune response. Humoral and cellular arms of this response neutralize free viruses and destroy infected cells leading to the recovery of the host. Nevertheless, virus-induced immune responses themselves may result in immunopathologic responses that initiate disease. Many questions concerning virus–immune sytem interactions are not yet resolved, although the immunovirology field has expanded enormously during the last year. This short report cannot detail all the known and documented possibilities as to how the immune system interacts with viruses; here only a few will be discussed. We will survey some published studies about the three-dimensional structure of viruses and antibody binding, that are very important in understanding how the humoral immune system can recognize viruses. Furthermore, we will describe some T cell reactions to various viruses and their relationship to MHC antigens. Finally, we will comment on some viruses which have important implications toward understanding autoimmune diseases.

Three-dimensional structures

The three-dimensional structures of some viral antigen epitopes have been resolved. These studies have aided our understanding of how the immune system can recognize and interact with viruses. The structure of a monoclonal antibody (mAb) Fab fragment bound to influenza virus neuraminidase is a salient example [1]. Colman et al [1] demonstrated that one of the antigenic epitopes is localized on surface loops of the neuraminidase molecule. Sequence changes within these loops diminished or abolished antibody-binding, confirming the correct localization of this antigenic determinant. Three-di-

mensional structure studies of influenza virus hemagglutinin (HA) [2] have added to the understanding of virus receptors and virus neutralization. The receptor-binding site of influenza virus HA forms a pocket surrounded by the antibody-binding sites. The close localization of these antibody-binding sites to the receptor-binding site suggests that antibody can neutralize influenza virus by sterically blocking receptor-binding sites.

Other investigators, using neutralization escape mutants, have studied the localization of biological important epitopes. Escape mutants are virus variants selected in the presence of neutralizing mAb. These variants do not bind the neutralizing mAb and thus escape neutralization. Normally the epitope of the neutralizing mAb has been previously determined. In most cases, single amino acid sequence changes in the mutants versus the original wild type virus can be demonstrated with amino acid or nucleic acid sequencing. Sixty-three antigenic poliovirus (Sabin) mutants, which escape the neutralization of 15 different mAbs, were selected and characterized to study interactions between the viral surface structures and humoral antibodies [3]. Localization of the amino acid changes were determined within the three-dimensional structure of these viral mutants. Most mutations were located within prominent protein structures, i.e. highly exposed regions on the viral surface. In addition, less exposed mutations affected local conformations, thus altering the antigenic epitopes. Page et al [3] have presented an interesting mechanism by which animal viruses can escape immune surveillance and neutralization. This is through decorations of a virus surface with loops and pockets that could be partially modified without disrupting structures necessary for virus integrity.

T cell reactions

Cytotoxic T lymphocytes (CTL) as well as T helper/ inducer cells are critical in the immune destruction of virus-infected cells and virus clearance from the infected host, and so play an important role in immune response to virus infection. Cytotoxic T cells express Lyt_2 on their surface and recognize their peptide regions in the presence

Abbreviations

CTL—cytotoxic T lymphocytes; EAE—experimental allergic encephalomyelitis; HA—hemagglutinin; HLA—human leukocyte antigen; Ig—immunoglobulin; LCMV—lymphocytic choriomeningitis virus; mAb—monoclonal antibody; MHC—major histocompatibility complex; RNP—ribonucleoprotein; RSV—respiratory syncytial virus.

of MHC class I molecules. T helper cells carry L_3T_4 determinant on their surface and recognize antigens presented with MHC class II molecules. Specific T cell subpopulations can be depleted using specific mAb to detemine the function of these cells.

The role of the T cells in lymphocytic choriomeningitis virus (LCMV) infection was examined by depleting either L_3T_4 $^+$ T cells or Lyt_2 $^+$ T cells [4]. Mice depleted of their Lyt_2 $^+$ T cells produced virtually no LCMV-specific CTL and were resistant to the immunopathologic disease after intracerebral inoculation with LCMV. However, mice treated only with anti-L_3T_4 antibodies, i.e. mAb to T helper cells, were fully susceptible to the LCMV immunopathologic disease. Their CTL response was about 10-fold lower than in control mice. In another study, Ahmed et al [5] examined the requirement of the L_3T_4 $^+$ T helper cells for the induction of a LCMV-specific CTL response. As above, depletion of Lyt_2 $^+$ T cells abolished the LCMV-specific CTL response and the ability to clear virus. However, depletion of T helper cells had only a minimal effect on the CTL response. The antiviral antibody response was markedly suppressed in these animals. These observations indicate that an anti-LCMV-specific CTL response can be generated even if there is a paucity of T helper cells. A lack of T helper cells appear to have a more severe effect on the humoral response than on the cellular immune response. These studies also support the contention that CTL plays an active role in controlling viral infections.

An additional model for studying viral T cell interactions is influenza virus infection of mice [6]. Influenza virus is known to undergo antigenic shift and drift. In this way virus may infect individuals immune to the previous strain of influenza virus. Nevertheless, T helper cells stimulated by influenza virus HA show a broader pattern of recognition than antibodies [7], which can then form a basis of a memory response to a new influenza virus infection. T helper cell clones are able to provide help in vitro to B cells for antibody production. Additionally, Lightman et al [8] demonstrated that Lyt_2 $^+$ cells are more efficient in viral clearance than L_3T_4 $^+$ T cells. Lyt_2 $^+$ cytotoxic T cells protected mice against lethal infection by influenza virus and were also able to limit virus spread.

Pathologic and protective immune responses can be adoptively transferred by lymphocytes [9]. Transferred Lyt_2 $^+$ T cells cleared respiratory syncytial virus (RSV) from acutely infected mouse lung more effectively than did L_3T_4 $^+$ T cells by an antibody-independent mechanism [10]. However, delayed transfer at 14 days after infection with primed L_3T_4 $^+$ T cells cleared lung RSV, which correlates with specific anti-RSV antibody production. These results indicate that two independent immune mechanisms are capable of RSV clearance: (1) an antibody-independent mechanism during the early stage of the infection, and (2) a L_3T_4 $^+$ T cell-triggered antibody mechanism later in the infection.

Some of the antigenic determinants recognized by cellular immune response have been well characterized [11]. A sequence of 10 amino acids from the Epstein-Barr virus-encoded membrane protein could be used to induce Epstein-Barr virus-specific CTL. This peptide is located within the plasma membrane of B lymphocytes transformed by the Epstein-Barr virus.

MHC molecules

All T cell reactions are known to be MHC dependent. MHC molecules are cell surface proteins determining the specificity of the cellular immune response. Antibody can bind to free virus, whereas T cell receptors recognize foreign antigens only when they are associated with a MHC molecule. The three-dimensional structure of the class I MHC antigen from human cells has been visualized as a large groove containing putative processed foreign peptide [12]. Viruses have the ability to induce the expression of MHC class I surface antigens. Neurotropic coronavirus infection [13] leads to MHC class I expression on the cell surface of oligodendrocytes and astrocytes. Suzumura et al [13] were able to induce MHC expression by the addition of supernatant fluid in tissue culture without transfering virus, suggesting that infected astrocytes release soluble factors that mediate the expression of class I MHC antigens. In another system, MHC class I antigens were demonstrated on hepatocyte membranes during chronic hepatitis B virus infection [14].

Class II MHC antigens are expressed on the surface of macrophages and B lymphocytes. They are responsible for antigen presentation on antigen-presenting cells [15]. Helper T cells recognize foreign peptides only in association with class II MHC molecules. Observations in cytomegalovirus infection [16] suggest that all three human class II families (DR, DQ and DP) are involved in T helper cell-dependent cytomegalovirus recognition.

Autoimmunity

Viruses have long been proposed to stimulate autoimmune response. Often during a virus infection antibodies to self proteins can be detected. Virus infections can initiate a non-specific general polyclonal reaction of the immune system. Some of the resulting immune responses may be directed against self antigens. Some viruses randomly infect B cells, which are then induced to differentiate and secrete antibody. Another possibility is autoimmunization with tissue proteins released from virus-infected cells leading to autoantibodies or generation and expansion of self reactive T cell clones. A third way of inducing autoimmune diseases is through molecular mimicry. The prediction is that the common determinant between a virus protein and a host epitope be at a disease-inducing site. The cross-reacting immune response may then increase the initial damage caused by the virus infection.

Recently, molecular mimicry could be demonstrated using mAb and even direct protein and nucleic acid se-

quence comparisons. Sequence homology between the U1 small nuclear ribonucleoprotein (RNP)-associated autoantigen and the p30^{gag} protein of type C retrovirus has been described [17]. These proteins also show immunological cross-reactivity. In addition, the authors were able to demonstrate antibody production to U1 RNP after immunization with the murine leukemia virus p30^{gag} protein. This suggests the importance of retrovirus in the initiation of autoimmunity, which may lead to rheumatic and connective tissue diseases.

Another disease which has autoimmune potential is human infectious mononucleosis. Infection with Epstein-Barr virus can lead to infectious mononucleosis that is characterized by a particularly high incidence of autoantibodies. Studies of immunoglobulin (Ig)M antibodies produced during acute infectious mononucleosis indicated that these antibodies recognized at least 10 cellular proteins [18]. All these autoantibodies were highly cross-reactive with each other. The binding could be inhibited by synthetic peptides consisting of the glycine-alanine repeating region of the Epstein–Barr virus nuclear antigen. Interestingly, sequence comparisons between the cross-reactive epitopes showed some variability indicating that not only the primary sequence but also the conformation was an important factor in defining the epitope.

Immunopathic myocarditis in mice is a good model for autoantibody production and disease [19]. Coxsackie B virus infection is associated with autoantibodies directed against cardiac myosin. Here mice susceptible to immunopathic myocarditis produced autoantibodies of the IgG class specific for cardiac myosin. These heart-specific autoantibodies are associated with myocarditis. Further autoantibodies of the IgM class that cross-react with heart, skeletal muscle and brain myosin were also found. The non-susceptible mouse strains produced only IgM and similar antibodies were present in non-infected mice, indicating that these IgM antibodies, in contrast to the IgG antibodies, may not have any clinical significance.

The type of virus-induced autoimmunity does not only depend on the virus strain but also on the host genetic composition. Myocarditis after Coxsackie B virus infection is not only dependent on the production of autoantibodies but also on cellular immune responses [20]. In vivo depletion of L_3T_4 $^+$ (T helper cells) and/or Lyt_2 $^+$ (cytotoxic/suppressor T cells) prevents myocarditis. In addition, the results suggest that cardiac injury in Balb/C mice is Lyt_2 $^+$ T cell-dependent, in DBA/2 mice is L_3T_4 $^+$ T cell-dependent and in A mice both L_3T_4 $^+$ and Lyt_2 $^+$ T cells are involved.

Immunological cross-reactivity can also be observed on the T cell level. A virus-induced CTL response can cross-react with host tissue. Human CTL response to measles virus that cross-react with myelin basic protein were generated [21]. The killing of these CTL could be enhanced by culturing these T cells with myelin basic protein during the killing assay. These measles-specific CTL had the ability to kill target cells coated overnight with myelin basic protein. Conversely, CTL generated by culturing the effector cells with myelin basic protein for 6 days could kill myelin basic protein coated target cells and measles

virus infected target cells. These results suggest a functional cross-reaction between myelin basic protein and measles virus in humans.

Class II MHC restricted T cell lines from rats with subacute measles encephalitis that initiate central nervous system disease have been characterized [9]. Myelin basic protein specific T cells obtained after infection did not response to measles virus infected cells and also measles virus specific T cells did not interact with myelin basic protein. Furthermore, adoptive transfer of these myelin basic protein specific T cells induced experimental allergic encephalomyelitis (EAE) in susceptible syngeneic rats. These results demonstrate that autoimmune reactions can arise in susceptible rats after measles virus infection without the necessity of cross-reaction at the T cell level. These results may be due to generation and expansion of central nervous system reactive T cells induced by virus infection.

Further studies of the interactions between various viruses and the immune system will provide additional insight into how the immune cells recognize virus, virus-infected or altered cells and/or their products. Such observations and findings will allow new avenues for the development of virus-specific therapies and vaccines as well as treatments for autoimmune disease.

Acknowledgement

Annotated references and recommended reading

●   Of interest
●●   Of outstanding interest

1.   COLMAN PM, AIR GM, WEBSTER RG, VARGHESE JN, BAKER AT,
●   LENTZ MR, TULLOCH PA, LAVER WG: How antibodies recognize virus proteins. Immunol Today 1987, 8:323–326.
The 3-dimensional structure of a monoclonal antibody Fab fragment bound to influenza virus neuraminidase is reviewed. Antigenic epitopes are localized surface loops.

2.   WEIS W, BROWN JH, CUSAK S, PAULSON JC, SKEHEL JJ, WILEY DC:
●   Structure of the influenza virus haemagglutinin complexed with its receptor, sialic acid. Nature 1988, 333:426–431.
The 3-dimensional structure of influenza virus hemagglutinin strengthens our understanding of virus receptors and virus neutralization.

3.   PAGE GS, MOSSER AG, HOGLE JM, FILMAN DJ, RUECKERT
●●   RR, CHOW M: Three-dimensional structure of poliovirus serotype 1 neutralizing determinants. J Virol 1988, 62:1781–1794.
63 antigenic poliovirus mutants are characterized. An interesting mechanism of how virus escapes neutralization is discussed.

4.   LEIST TP, COBBOLD SP, WALDMANN H, AGUET M, ZINKERNAGEL
●   RM: Functional analysis of T lymphocyte subsets in antiviral host defense. J Immunol 1987, 138:2278–2281.

The function of T lymphocytes in LCMV infection is examined.

5. AHMED R, BUTLER LD, BHATTI L: T4+ T helper cell function
•• in vivo: differential requirement for induction of antiviral cytotoxic T cell and antibody responses. J Virol 1988, 62:2102–2106.

LCMV specific CTL response can be produced even with a deficiency of T helper cells. This has a more severe effect on antibody production, rather than on the cellular immune response.

6. WRAITH DC: The recognition of influenza-A virus-infected
• cells by cytotoxic T lymphocytes. Immunol Today 1987, 8:239–246.

A review on T cell functions after influenza virus infection.

7. BROWN LE, KATZ JM, FRENCH RA, ANDERS EM, WHITE DO: Char-
• acterization of subtype-specific and cross-reactive helper-T cell clones recognizing influenza virus hemagglutinin. Cell Immunol 1987, 109:12–24.

T helper cells stimulated by influenza virus HA may provide a basis for a rapid memory response.

8. LIGHTMAN S, COBBOLD SP, WALDMANN H, ASKONAS BA: Do
• L3T4+ T cells act as effector cells in protection against influenza virus infection. Immunology 1987, 62:139–144.

Cytotoxic T cells are more efficient in influenza virus clearance than T helper cells.

9. LIEBERT UG, LININGTON C, TER MEULEN V: Induction of autoim-
• mune reactions to myelin basic protein in measles virus encephalitis in Lewis rats. J Neuroimmunol 1988, 17:103–118.

Myelin basic protein-specific T cell clones from rats with subacute measles encephalitis do not cross-react with measles virus and their adoptive transfer can induce EAE.

10. CANNON MJ, STOTT EJ, TAYLOR G, ASKONAS BA: Clearance of
• persistent respiratory syncytial virus infections in immunodeficient mice following transfer of primed T cells. Immunology 1987, 62:133–138.

RSV can be cleared by 2 different immune mechanisms depending on the stage of the infection.

11. THORLEY-LAWSON DA, ISRAELSOHN ES: Generation of specific
• cytotoxic T cells with a fragment of the Epstein-Barr virus-encoded p63/latent membrane protein. Proc Natl Acad Sci USA 1987, 84:5384–5388.

A 10-amino acid long peptide can induce Epstein-Barr virus specific CTL and therefore contains an eptiope for T cell recognition.

12. BJORKMAN PJ, SAPER MA, SAMRAOUI B, BENNETT WS, STROMINGER
•• JL, WILEY DC: Structure of the human class I histocompatibility antigen, HLA-A2. Nature 1987, 329:506–511.

The 3-dimensional structure of HLA molecules has long been sought, in order to develop specific insight into the antigen and T cell recognition properties of these molecules.

13. SUZUMURA A, LAVI E, BHAT S, MURASKO D, WEISS SR, SILBERBERG
• DH: Induction of glial cell MHC antigen expression in neurotropic coronavirus infections: characterization of the H-2-inducing soluble factor elaborated by infected brain cells. J Immunol 1988, 140:2068–2072.

MHC class I expression can be induced on the surface of glial cells by neurotropic coronavirus.

14. CHU C-M, SHYU W-C, KUO R-W, LIAW Y-F: HLA class I antigen
• display on hepatocyte membrane in chronic hepatitis B virus infection: its role in the pathogenesis of chronic type B hepatitis. Hepatology 1987, 7:1311–1316.

Chronic hepatitis B virus infection leads to expression of HLA class I antigen on hepatocytes and cytotoxic T cells are HLA class I antigen restricted.

15. TODD JA, ACHA-ORBEA H, BELL JI, CHAO N, FRONEK Z, JACOB
•• CO, MCDERMOTT M, SINHA AA, TIMMERMAN L, STEINMAN L: A molecular basis for MHC class II-associated autoimmunity. Science 1988, 240:1003–1009.

Class II MHC and their immunoregulatory role is explained on a molecular level.

16. GEHRZ RC, FUAD S, LIU Y-NC, BACH FH: HLA class II restric-
• tion of T helper cell response to cytomegalovirus (CMV). I. Immunogenetic control of restriction. J Immunol 1987, 138:3145–3151.

All 3 HLA class II families are involved in cytomegalovirus recognition.

17. QUERY CC, KEENE JD: A human autoimmune protein asso-
• ciated with U1 RNA contains a region of homology that is cross-reactive with a retroviral P30gag antigen. Cell 1987, 51:211–220.

A sequence homology between the small nuclear RNP autoantigen and a retrovirus protein enhances the importance of retroviruses for autoimmune diseases.

18. RHODES G, RUMPOLD H, KURKI P, PATRICK KM, CARSON DA,
• VAUGHAN JH: Autoantibodies in infectious mononucleosis have specificity for the glycine-alanine repeating region of the Epstein-Barr virus nuclear antigen. J Exp Med 1987, 165:1026–1040.

IgM autoantibodies produced during acute infectious mononucleosis recognize at least 10 cellular proteins.

19. NEU N, BEISEL KW, TRAYSTMAN MD, ROSE NR, CRAIG SW: Au-
• toantibodies specific for the cardiac myosin isoform are found in mice susceptible to coxsackievirus B3-induced myocarditis. J Immunol 1987, 138:2488–2492.

Mice strains susceptible to immunopathic myocarditis produce autoantibodies to the IgG class specific for cardiac myosin (genetic factors).

20. LODGE PA, HERZUM M, OLSZEWSKI J, HUBER SA: Coxsackievirus
• B-3 myocarditis: acute and chronic forms of the disease caused by different immunopathogenic mechanisms. Am J Pathol 1987, 128:455–463.

T cell depletion studies demonstrate that virus-induced autoimmunity depends not only on the virus strain, but also on the host genetic composition.

21. MATOSSIAN-ROGERS A, DOS SANTOS A, FESTENSTEIN H: Human
•• cytotoxic T cells against measles virus-infected and myelin basic protein-coated targets are cross-reactive. Int Arch Allergy Appl Immunol 1987, 84:159–164.

Immunological cross-reaction leading to autoimmune events at the T cell level.