

Some aspects on immunopathological mechanisms in persistent viral infection

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ABSTRACT

How does viral persistence develop, and what are its effects? Viruses can persist for years without provoking an effective host immune response or otherwise causing the cell destruction characteristic of an acute viral infection. Mutations in viral genomes that affect T-cell-receptor recognition by CD8⁺ cytotoxic T lymphocytes have been shown to allow viral evasion from immune surveillance during persistent viral infections. Although CD4⁺ T-helper cells are crucially involved in the maintenance of effective cytotoxic T-lymphocyte and neutralizing antibody responses, their role in viral clearance is unclear. Viral escape from CD4⁺ T lymphocytes is a possible mechanism of virus persistence. The reducing cell surface expression of viral glycoproteins, viruses can also inhibit MHC expression by infected cells, thereby protecting against CD8⁺ cytotoxic T-lymphocyte (CTL) recognition and lysis.

Key words: immunity, immunopathology, persistent viral infection

Persistent virus infections are increasingly being recognized as a significant cause of human morbidity and mortality. Viral infections also elicit immune and inflammatory responses. Although many viral infections are short-term, others persist in a chronic active state, other times latent with subsequent reactivation. Viruses cause infection by invading cells of the body and multiplying within them. Within their life cycle they have a relatively short extracellular period, prior to infecting the cells, and a longer intracellular period during which they undergo replication. Natural killer (NK) cells become activated during viral infections. The virus persists in many cell

types, including lymphocytes and macrophages. Lymphocytes, macrophages, and neutrophils are all capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) against virus infected cells. The lymphocytes with this ability appear to be heterogeneous. Natural killer cells, as well as null lymphocytes with Fc receptors for IgG, appear to be able to mediate ADCC activity (1-6). □

I mmunological memory is an exclusive property of the acquired immune system, where in the presence of CD4 T cell help, T cells and B cells clonally expand and differentiate to provide effector systems that protect the host from pathogens.

Cell mediated immune responses are a major determinant in the pathogenesis of viral infections. The functions of antigen specific T lymphocytes are required for recovery from viral infections, for clearance of virus or control of persistent infection. On the other hand, an antiviral immune response may also result in immunopathology when an inflammatory response destroys cells infected by a relatively non cytopathic virus.

Immune-mediated disease may develop in certain virus infections in which viral antigens and uncontrolled immune hypersensitivity to them persist for a long period. Immune-mediated disease can be mediated by both humoral and cell-mediated immune functions. Immune-complex syndrom can be mediated by virus/virus antigen antibody complexes. T cells (cytotoxic and helper) can also mediate immunopathologic injuries via a number of mechanisms (7-12).

The hepatitis B virus (HBV) and the hepatitis C virus (HCV) cause acute and chronic liver disease, cirrhosis, and hepatocellular carcinoma. By killing infected cells and producing antiviral cytokines capable of purging HBV from viable hepatocytes, cytotoxic T-lymphocytes (CTLs) are also thought to eliminate the virus. The incidence of hepatitis B surface antigen was especially high in patients with vasculitis of the polyarteritis nodosa group. In other studies antibodies against hepatitis C virus have been detected in 70-100% and viraemia found in 86% of patients with mixed type II cryoglobulinemia.

Parvovirus infections are associated with collapsing glomerulopathy, idiopathic focal segmental glomerulosclerosis (FSGS). Coxsackie virus can associate with IgA nephropathy, whereas polyoma BKV and hantavirus have been found mainly associated to tubulo-interstitial nephritis, and only occasionally show glomerular involvement. HBV-associated GN pathogenesis has not been defined completely (13-14).

Cellular immune responses are also likely to determine the outcome of HCV infection, but the dynamics of such responses and their

relationship to viral clearance and persistence are poorly understood. It is widely believed, however, that HCV is noncytopathic and that immunologically mediated events play an important role in HCV pathogenesis, although the mechanisms whereby HCV causes acute and chronic hepatitis are still unclear. Hepatitis C virus (HCV) infection has been reported to be associated with a wide range of immunologic markers. Th1 cytokines positively correlate with hepatic inflammation in chronic hepatitis B virus (HBV) infection. The pro-inflammatory cytokines IL-6 and IL-18 are involved in viral clearance and in metabolic and viral hepatic diseases, respectively. In HCV+ and HBV+ patients there are higher levels of Th1 cytokines, particularly in the course of chronic hepatitis B, and that IL-18 and IL-6 levels may have important roles as markers of both inflammation and hepatic injury, particularly in the course of hepatitis C. It has been shown that the onset of viral clearance and liver disease coincide with the onset of the CD8⁺ T cell response and the entry of virus-specific CD8⁺ T cells into the liver, and that primary failure to induce a T cell response or functional exhaustion of an initially vigorous T cell response are associated with viral persistence. Importantly CD8⁺ T cell-mediated destruction of infected cells is probably not the only way to eliminate the virus because viral clearance can occur in the absence of liver disease as long as antiviral CD8⁺ T cells are present and produce antiviral cytokines such as IFN- γ . HCV is a strong inducer of type 1 interferon but it is relatively resistant to its antiviral activity. The virological and immunological basis for the survival of HCV in the face of a CD8⁺ CTL response is unclear at the moment. Future studies aimed at defining the mechanisms whereby HCV can evade or suppress the immune response and establish chronic infection are clearly warranted.

The cellular immune response to hepatitis C virus (HCV) plays a critical role in determining the clearance or persistence of HCV. Moreover, in chronic HCV infection, these responses that are insufficient to eradicate virus completely may cause liver injury. There is no relationship between T cell responses and the parameters of disease evolution as determined by ALT (serum alanine transaminase levels), but

there is a positive relationship between the presence of a core-specific T cell responses and the viremia.

The results suggest that although the infection can be controlled to varying degrees by the destruction of infected cells, full control of the infection may also involve noncytolytic T cell effector functions such as the production of antiviral cytokines (15-18).

In the case of cytotoxic T-lymphocyte (CTL) responses to persistent viral infections, pathology may arise as a consequence of cell destruction directly by the virus or indirectly due to the CTL response, leading to maximum pathology at intermediate efficacy of the immune response.

Some viruses persist, and the immune responses may become detrimental to the host and cause immune-mediated disease. When an antigen (virus) persists, pathologic changes and diseases result from different types of immunologic interactions, including immediate hypersensitivity, antibody-mediated immune complex syndrome, and tissue damage caused by cell-mediated effector cells and antibody plus complement. Antibodies may neutralize virus directly or destroy virus-infected cells via ADCC or complement.

Clinical manifestations of chronic viral infections may reflect pathology caused by the virus or by the host response to eliminate cells harboring a virus. Infection with HIV is associated in the majority of cases with the production of virus specific antibody, some of which can be shown to neutralize the virus in vitro. There is a strong virus specific CTL response to the virus in the majority of patients. The CTL response does not appear able to clear the virus, however, and persistent infection follows. How does HIV manage to persist in the face of such a strong antiviral immune response? Like many persistent viruses, HIV has a number of strategies for evading the host's immune response. One of the most important of these is the ability to undergo "antigenic variation" the ability to mutate key epitopes which are recognized by the immune response.

Infection with cytomegalovirus (CMV) is ubiquitous within the human population. Cytomegalovirus seropositivity may be associated with a decrease in immune responses to heterologous viruses and this may have clinical consequences for the healthy elderly individual. Cytomegalovirus has been associated with the increased production of rheumatoid factor, antiphospholipid antibodies, cold agglutinins, antimyosin antibodies, anti-endothelial cell antibodies, and antiganglioside antibodies. Cytomegalovirus infection induces these autoantibodies infrequently and autoimmune disease associated with CMV infection is probably rare.

Neutralizing antibodies induced by CMV are directed primarily against the major envelope protein of CMV, glycoprotein B (gB). Antibodies to CMV gB share some homology with rheumatoid factor, thus providing a theoretical relationship between CMV infection and autoimmune disease. Recently, it was reported an increased incidence of antibodies to ribonucleoprotein (RNP) among naturally CMV-infected individuals, as well as an increase in antibodies to U1-70 kD. Mixed encephalitic viral infections have been reported with cytomegalovirus (CMV) and adenovirus, echovirus and measles, respiratory syncytial virus (RSV) and herpes simplex virus (HSV).

Subacute encephalitis is seen in up to 30% of patients with AIDS, and CMV may be the causal agent in some cases. The two viruses often coexist in brain specimens taken from AIDS patients.

While clinical infections by human herpesvirus-6 (HHV-6) and Epstein-Barr virus (EBV) are generally silent or mild, serious overt disease may occur. Both HHV-6 and EBV are known to produce neurologic complications. While CNS complications are generally infrequent with EBV infections, they may be the only clinical finding. Central nervous system (CNS) disease can be seen with HHV-6, with convulsions being the most common manifestation. In contrast, less than 1% of EBV infections are associated with central nervous system disease. Encephalitis, Guillain-Barré syndrome, aseptic meningitis, facial palsy, cerebellar ataxia,

transverse myelitis, and Bell's palsy are the most frequently reported CNS complications associated with EBV infections. Concurrent HHV-6 and EBV infections with neurologic complications may occur more frequently than generally appreciated.

Reactivation of latent EBV and HHV-6 infections occur in HIV-1 induced immunodeficiency syndrome and may produce autoimmune phenomena and lymphoproliferative lesions. The mechanism of neurologic injury from EBV may be the result of infected lymphocytic cells infiltrating neural tissue or

inducing an inflammatory reaction which secondarily causes symptoms.

Lymphocytic choriomeningitis virus (LCMV) can infect cells of the immune system, establish suppression of cellular and humoral immunoresponses, and cause persistent infection in its natural host (19-20).

Understanding the mechanism by which viruses persist and escape immune surveillance is a key for defining measures to control and eliminate the infections and diseases they cause. Viruses that persist often interfere with the differentiated function of infected cells. □

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