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Autoantibodies in Viral Infections

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Abstract

The immune system's ability to distinguish self from nonself is essential for initiating host defense against microbial antigens and protection of self-antigens from autoimmune-associated destruction. Virus infections have been implicated in the initiation of multiple human autoimmune diseases. This chapter aims to summarize the main principles for some specific viral infections and the subsequent production of autoantibodies resulting in the initiation, progression, and perpetuation of autoimmune diseases. Various mechanisms by which virus infections can induce autoimmune responses including molecular mimicry and epitope spreading are discussed with respect to these viruses, and evidence implicating virus infections in the pathogenesis of various human autoimmune diseases is reviewed. A better understanding of the viral origin of autoimmune diseases is an important step in the identification of high-risk patients as well as designing prevention and disruption strategies.

Keywords: autoimmune disease, autoimmunity, virus, Epstein-Barr virus, cytomegalovirus, hepatitis B virus

1. Introduction

An autoantibody is an antibody produced in response to a constituent of one's own cells or in other words produced against self-antigens such as nucleic acids, proteins, carbohydrates, lipids, and other multimolecular complexes. Autoantibodies may be organ-specific or systemic and are a characteristic feature of autoimmune disease (AD). Autoantibodies may also be produced as a result of different causes such as cancer, infection, or drug-related reactions [1]. The diagnosis and classification of autoimmune diseases (ADs) depends on serum autoantibodies out of which some specific ones have a prognostic significance and are thus

used as markers to determine disease activity. Prior to clinical manifestation of an established AD, asymptomatic individuals may carry autoantibodies for many years. In such cases, the serological detection of these antibodies exhibits a strong predictive value [2–5].

2. Autoantibodies in viral disease

It is well established that there is often an association of transient, low-titer, polyspecific auto-antibodies with common viral infections [6]. Autoantibodies may be detected in a variety of viral illnesses including hepatitis A, B, and C, parvovirus B19, enteroviruses, cytomegalovirus (CMV), and Epstein-Barr viruses (EBV) [1, 7–11]. Infectious agents have been implicated as an initial environmental trigger of AD in general, and in the induction of autoantibodies specifi-cally [12–17]. It has been suggested that transient autoimmune responses are induced by acute viral infections in children and adults. Such responses may include generation of transient autoantibodies of typically low titer. The progression of such an immune state to an established autoimmune disease is rare [6, 18] as usually virally induced autoantibodies typically resolve with time. Hence, it may be difficult to differentiate autoimmune disease and self-limited illness.

Some of the commonly tested autoantibodies in viral infections include antinuclear antibod-ies (ANAs), antibodies directed against DNA, antibodies against proteins that bind to nucleic acids i.e. extractable nuclear antibodies (ENA), those directed against phospholipids, and anti-neutrophil cytoplasmic antibodies (ANCAs). In addition to these, the immune system may produce antibodies specific to certain tissues or organs (e.g., against hepatic, renal, gastric, intestinal, thyroid, pancreatic, muscular, testicular, dermatological, or neurological tissues). Also, the tendency of some viral infections to induce inflammatory responses in a variety of organ systems may also result in the development of autoimmune conditions. Hepatitis C and B virus, human immunodeficiency virus, parvovirus B19, cytomegalovirus, and Epstein-Barr virus appear to be associated with autoantibodies more commonly than other viruses.

2.1. Mechanism

The mechanisms responsible for the generation of autoantibodies as a result of viral infections remain unclear. A few proposed mechanisms include cross-reactivity between viral proteins and autoantigens [19], molecular mimicry [16, 17, 20], and the induction of apoptosis of virus-infected cells [21], all leading to the production of autoantibodies. Another theory suggests that autoantibodies are anti-idiotypic antibodies to antiviral antibodies [22]. However, molec-ular or antigenic mimicry between microbial proteins and self-components (i.e., proteins, carbohydrates, or DNA epitopes) remains the most likely mechanism of autoimmunity post viral infection [20, 23].

3. Viruses and autoimmunity

The existence of autoantibodies that do not induce tissue damage is known [19]; however, most of them are known to have clear pathogenic effects [24]. Pathogenic effects can vary from modu-lation of the biological activities such as cytotoxicity, phagocytosis and cell surface receptor

binding, immune complex (consisting of viral antigen and antiviral antibodies)-mediated damage, and even lysis of the cell [24]. Although investigations into the relationship between viruses and the development of autoantibodies are ever continuing, we will focus on three different viruses that appear to be associated more commonly with autoimmunity than other viruses: Epstein-Barr virus (EBV), hepatitis B virus (HBV), and cytomegalovirus (CMV).

3.1. Epstein-Barr virus

Epstein-Barr virus (EBV) is a double-stranded DNA member of the gamma-herpesvirus family and is considered to be one of the most sinister members of the herpesvirus family. It usually infects young adults, adolescents, or children. EBV attacks and persists in B lymphocytes and based on viral antigen expression is known to exhibit up to four types of latency (latency 0–3). Upon reactivation from latent to lytic stage, the production of a large number of infectious virions leads to host cell lysis.

Autoantibodies can be detected during infectious mononucleosis, the symptomatic primary infection of EBV, and various other lymphoproliferative diseases caused by EBV [8, 25]. In some circumstances, it is known to cause many different systemic autoimmune diseases. However, the most widely understood relationship between this infamous infecting agent and another autoimmune disease is between EBV and systemic lupus erythematosus (SLE), which is often exhibited through a high prevalence of the virus in the sera of patients. Although several viral pathogens have been known to be associated with SLE, Epstein-Barr virus is considered to be one of the most important environmental factors in the etiology of this autoimmune disease. The serological correlation has been well established over the years [26] with modern diagnostic methods producing similar results [27].

Identification of a specific viral antigen that induces production of SLE-specific autoantibodies has proven to be difficult as the sera of patients with SLE can often exhibit more than 100 different autoantibodies [28]. Mechanisms responsible for EBV-associated SLE include molecular mimicry, bystander activation, and epitope spreading [29]. Molecular mimicry remains the most well-established method by which EBV infection is known to cause SLE [30]. EBV-associated autoimmunity is thus known to be caused by cross-reacting viral and endogenous proteins. It has also been well investigated that the immune response against EBV and EBV nuclear antigen 1 (EBNA-1) is different between patients with SLE and healthy controls. Whereas healthy controls maintain a partial humoral response and generally do not produce long-standing cross-reactive antibodies, patients with SLE exhibit humoral immune response to EBNA-1 with the generation of cross-reactive antibodies only in susceptible individuals [30]. Autoantibody complexes may also arise due to binding between SLE-specific autoantigens Sm and Ro and circulating anti-EBNA-1 antibodies, due to structural similarities. Furthermore, epitope spreading as a result of autoantibody complex accumulation will result on overt clinical disease [31, 32]. Apart from Ro and Sm, EBNA-1 may also elicit creation of anti-dsDNA, another SLE-associated autoantibody, also via molecular mimicry [32].

Another hypothesis suggests that B cells expressing the EBV-encoded protein latent membrane protein 2A bypasses normal tolerance checkpoints and induces hypersensitivity to Toll-like receptor stimulation, further activating anti-SmB cells through the B-cell receptor/Toll-like receptor pathway. Eventually, this leads to increased proliferation or differentiation of antibody-secreting cells or both [33]. A third hypothesis suggests that during primary infection, autoreactive B cells

become infected by EBV and proliferate to become latently infected memory B cells. Since they express virus-encoded antiapoptotic molecules, these become resistant to normal B-cell homeostasis-associated apoptosis [34]. These impaired B cells activate autoreactive T cells which similarly fail to undergo apoptosis as they receive a costimulatory survival signal from infected B cells. The autoreactive T cells expand to produce cytokines, which recruit other inflammatory cells, resulting in target-organ damage and chronic autoimmune disease [35].

The association of EBV with rheumatoid arthritis is less clear. Patients with RA have higher levels of anti-EBV antibodies than healthy controls. Additionally, EBV-specific suppressor T-cell function is defective in rheumatoid arthritis, and patients with rheumatoid arthritis have a higher EBV load in peripheral blood lymphocytes. However, there is no clear evidence for the creation of rheumatoid arthritis-specific autoantibodies [36]. It has been proposed that EBV can, perhaps, play a role in the citrullination of autoantigens or the formation of auto-antibodies such as anticyclic citrullinated peptide, but this theory remains to be proven [37].

Graves' disease is another autoimmune disease which is the most common cause of hyperthyroidism. It has been hypothesized by Nagata et al. that the reactivation of persisting Epstein-Barr virus in B lymphocytes induces differentiation of host B cells into plasma cells [38]. B cells infected with EBV possess thyrotropin receptor antibodies (TRAbs) on the surface of immunoglobulins (Igs) [39]. EBV reactivation induces these TRAb+EBV+ cells to produce TRAbs. Activation of B cells infected with the virus by polyclonal B cell activation leads to the production of Igs through plasma cell differentiation. This may be induced by EBV reactivation. EBV-LMP1 enables B cells to produce every isotype of Ig. Thus, it has been hypothesized that EBV rescues autoreactive B cells to produce autoantibodies, which contribute to the development and exacerbation of autoimmune diseases including Graves' disease [38].

3.2. Cytomegalovirus

Human cytomegalovirus (HCMV) or cytomegalovirus (CMV) is a large double-stranded DNA prototypic pathogenic member of the beta-subgroup of the herpesvirus family. Certain features attributed to the cytomegalovirus, like lytic replication in several different tissues, its lifelong persistence through periods of latency and reactivation, an extraordinarily large proteome, considerable manipulation of adaptive and innate immune systems, and its worldwide prevalence in human populations, make it a prominent candidate for involvement and exacerbation of autoimmune abnormalities [40]. Cytomegalovirus is known to be a leading cause of mental retardation and congenital hearing loss, and CMV infection is known to induce several autoimmune disorders in mice that resemble abnormalities in SLE [41]. It has also been implicated in the development and/or progression of SLE in humans [42]. Additionally, CMV has been associated with many other autoimmune diseases such as inflammatory bowel disease [43], diabetes mellitus [44, 45], systemic sclerosis [46], antiphospholipid syndrome [47, 48], and rheumatoid arthritis. The relationship between CMV infection and accelerated atherosclerosis [49, 50] is unclear, as conflicting data have been reported, and thus requires further investigation. A clear relationship between HCMV seroprevalence and disease has not been established. A higher prevalence of HCMV IgG antibodies would be expected in patients suffering from specific types

of autoimmune diseases if HCMV is a causative agent for the onset of autoimmunity. The UL83-encoded pp65 matrix protein has been linked to autoantibodies in SLE patients [40]. Studies have found either higher HCMV-specific IgG titers [51] or higher frequencies of HCMV infection in patients with SLE [51, 52]. Moreover, in SLE patients with higher HCMV-specific IgG titers, more frequent autoantibodies could be detected [53, 54]. However, a clear cause-and-effect relationship between CMV infection and the creation of autoantibodies has yet to be ascertained. In a study of patients with SLE and some other autoimmune diseases such as Sjögren's syndrome, antiphospholipid syndrome, systemic sclerosis, biliary cirrhosis, polymyositis, or different types of vasculitis, a higher prevalence of CMV-associated IgM antibodies was detected [52]. The role of CMV in the pathogenesis of various autoimmune diseases requires further investigation.

3.3. Hepatitis B virus

Hepatitis B virus (HBV) is a small partially double-stranded circular DNA virus that replicates in the liver cells. This hepatotropic virus is classified in the Hepadnaviridae family. HBV remains one of the major causes of liver disease, varying in severity from person to person [53–56]. The most common autoimmune diseases associated with chronic HBV infection are membranous glomerulonephritis and systemic necrotizing vasculitis [57]. HBV uses active immune evasion strategies that target the adaptive response responsible for the elimination of HBV virus [55, 58]. CD4 T cells or helper T cells produce cytokines and are involved in the efficient development of effector cytotoxic CD8 T-cell antibody production by B cells. HBV-infected hepatocytes are cleared by CD8 T cells through both cytolytic and noncytolytic mechanisms, leading to a reduction in the levels of circulating virus. The B-cell antibody production neutralizes free viral particles and can also prevent infection or reinfection [55]. Liver injury during the acute and chronic phases of viral hepatitis may be caused by T-cell responses. HBV-specific CD8$^+$ T cells play a double role. On the one hand, the HBV-specific CD8$^+$ T cells are vital in the clearance and control of the virus, but on the other hand, when overall antiviral immunity is not robust enough to clear the viruses, liver tissue damage may occur through different pathways, including perforin-mediated cytotoxicity and Fas ligand/Fas-mediated apoptosis [59, 60]. Thus, liver damage in patients with chronic HBV infections may be a result of autoreactivity.

Antibodies against the asialoglycoprotein receptor-R have been reported in patients with chronic HBV [60]. The occurrence of antiasialoglycoprotein receptor-R antibodies in patients with moderate and severe chronic active hepatitis suggests that these antibodies are related to progressive liver damage development in patients with HBV infection rather than as simply a response to tissue damage. Either the host's immune response to virus-infected hepatocytes could result in liver damage [61] or this may be the effect of virus-induced apoptosis [21]. Autoantibodies produced as a direct result of this damage may be of various different kinds such as antiasialoglycoprotein receptor-R [60], antinuclear antibody [61], smooth muscle antibody [62, 63], antimitochondrial antibody [62], microsome antibody [62], rheumatoid factor [41], and proliferating cell nuclear antigen [61]. These autoantibodies bind to liver and kidney tissue and are directed against microsomal targets (expressed in estrogen receptor of these two organs) [64]. Further investigations are required to determine the cause-and-effect relationship between HBV and the generation of autoantibodies.

4. Conclusions

Viruses remain just one of the many etiological factors such as environmental stimuli, infection, genetic predisposition, cytokine activity, etc., which contribute to the development of autoimmune disease. Of the many mechanisms by which an infecting agent can induce an autoimmune reaction, molecular mimicry is probably one of the most common in viral-induced immunity. Over time, the development of chronic viral infections contributes to the development of a defective immune system, the accumulation of which gives rise to overt clinical illness. Thus, the study of infectious agents that play a role in the pathogenesis of this process is not only important to identify high-risk patients but also necessary in preventing the process of disease through medications. Prevention of such autoimmune abnormalities in general and virus-associated autoimmune phenomena in particular would be a great achievement in the field of autoimmunity.

Conflict of interest

The authors declare no conflict of interest.

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