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Hepatitis B Virus (HBV) and Autoimmune Disease

Ram Maya · M. Eric Gershwin · Yehuda Shoenfeld

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Abstract The etiology and pathogenesis of autoimmune diseases have long been an enigmatic subject that have involved genetic and environmental factors. Recent intriguing data has contributed to the mechanisms involved, including the relationship of infectious agents and loss of tolerance. This loss of tolerance is illustrated by the data on the immune response to Hepatitis B virus such as the molecular mimicry between HBV antigens and self proteins, the generation of immune complexes between HBV antigens and antibodies, and apoptosis/tissue damage resulting in the exposure of intracellular antigens to the immune system. In this paper, we review the current database related to HBV infection and a variety of autoimmune conditions, including autoimmune hepatitis, systemic lupus erythematosus, aplastic anemia, antiphospholipid syndrome, polyarteritis nodosa, rheumatoid arthritis, type 1 diabetes, multiple sclerosis, thyroid disease and uveitis.

R. Maya · Y. Shoenfeld (✉)
Department of Medicine 'B' & Center for Autoimmune Diseases,
Chaim Sheba Medical Center,
Tel-Hashomer 52621, Israel
e-mail: shoenfel@post.tau.ac.il

M. E. Gershwin
Division of Rheumatology, Allergy and Clinical Immunology,
University of California,
Davis, CA 95616, USA

Y. Shoenfeld
Sackler Faculty of Medicine, Incumbent of the Laura
Schwarz-Kip Chair for Research of Autoimmune Diseases,
Tel-Aviv University,
Tel-Aviv, Israel

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Abbreviations

HbsAg	hepatitis B surface antigen
HbsAb	hepatitis B surface antibody
HbcAb	hepatitis B core antibody
HbeAg	hepatitis B e antigen
HbeAb	hepatitis B e antibody
HBx protein	hepatitis B × protein
AID	autoimmune disease
MS	multiple sclerosis
APS	antiphospholipid syndrome
RA	rheumatoid arthritis
SLE	systemic lupus erythematosus
GN	Glomerulonephritis
MN	membranous nephropathy
PAN	polyarteritis nodosa
AIH	autoimmune hepatitis
T1D	type 1 diabetes
EAE	experimental autoimmune encephalomyelitis
MBP	myelin basic protein
aCL	anticardiolipin
b2GPI	b2-glycoprotein I
RF	rheumatoid factor
CCP	cyclic citrullinated peptide
ANA	antinuclear antibodies
SMA	smooth muscle antibodies
LKM1	Liver/kidney microsomes type 1

Introduction

The immune system's ability to distinguish self from non-self is the basis for the physiology and ontogeny of immunity and is essential for both host defense against microbial antigens and protection of self antigens from autoimmune destruction [1]. Autoimmune diseases are characterized by the presence of auto-reactive lymphocytes in affected tissues and circulating autoantibodies, immunoglobulins reacting against self-antigens [2]. The occurrence of autoimmunity is clearly the consequence of the combination of genetic and environmental factors; therefore, numerous investigations have been devoted to the search of the environmental component controlling the onset of autoimmune diseases. Clinical and epidemiological evidence have long pointed to infection as a trigger of autoimmune disease [3–8]. Clearly, other environmental factors are also implicated, i.e., chemicals, but these will not be discussed herein. Hepatitis B virus (HBV) is one of the viruses that has significant data on the relationship with loss of tolerance and therefore will be the major subject of this review [8].

Hepatitis B Virus

Hepatitis B is a small, partially double-stranded circular DNA virus that favors replication in liver cells. Therefore, it is termed a hepatotropic virus classified in the hepadnaviridae family. Hepatitis B virus is the major cause of liver disease that varies greatly in severity from person to person [9–11] and has a wide geographic bias, with the largest number of cases in Asia. Some subjects control HBV efficiently and clear virus from the bloodstream either without clinically evident liver disease, or with acute inflammation of the liver that resolves without long-term clinical *sequellae*. Other patients fail to clear the virus and develop chronic infection. Most chronically infected patients remain largely asymptomatic without life-threatening liver disease but 10–30% develop liver cirrhosis with possible progression to liver cancer [9–13].

HBV Epidemiology

Despite the existence of hepatitis B vaccination, HBV infection is still prevalent worldwide. Hepatitis B virus currently infects more than 300 million people worldwide and accounts for significant morbidity and mortality [10, 11, 14]. Virus is transmitted by different ways, which include vertical (mother to child or generation to generation through close contact and sanitary habits), early life horizontal transmission (through bites, lesions, and sanitary habits), and adult horizontal transmission (through sexual contact, intravenous drug use, and medical procedure exposure) [15].

The global epidemiology of HBV infection has traditionally been described according to three categories of endemicity—high, intermediate, and low, depending on the proportion of the population that is seropositive for HBsAg. HBsAg seroprevalence has marked geographic variations, and Table 1 lists the endemicity of the virus in different areas of the world [9].

HBV has different viral genotypes analyzed by nucleotide sequence; the geographic distribution, epidemiology, and clinical themes of HBV have been investigated according to these different HBV genotypes (Table 2) [14, 16, 17].

Structure and Seromarkers of HBV

The intact, infectious virus is 42–47 nm in diameter and composed of an inner core termed nucleocapsid covered with an envelope (Fig. 1; Table 3). The nucleocapsid contains hepatitis B core antigen (HBcAg) which is a major structural component of the nuclear capsid, Hepatitis B e antigen (HBeAg) that is a secreted form of the viral core antigen and not required for HBV replication or infection, an incomplete double-stranded DNA molecule and a DNA polymerase with reverse transcriptase activity. The envelope is composed mainly of lipids and hepatitis B surface antigen (HBsAg) which is found both on the surface of the virus and as self-assembling, noninfectious spherical or tubular particles [9, 12, 15, 16, 18].

Immune Response

After infection, the virus enters the liver via the bloodstream, binds to surface receptors of hepatocytes, and enters the cell. Viral core particles migrate to the nucleus of the hepatocyte where it uses host RNA polymerase II for the transcription of the virus mRNA which then is translated to the cytoplasm to produce the viral surface,

Table 1 HBV endemicity

Endemicity	Areas of endemicity
High (HBsAg≥8%)	China, Indonesia, Nigeria and much of the rest of Asia and Africa. Western Amazon basin, including Brazil, Peru and parts of Colombia
Intermediate (2%≤HBsAg≤7%)	Southern Europe, the Middle East, and South Asia
Low (HBsAg≤2%)	Most of Central and South America

Table 2 Geographic distributions of HBV based on genotype

Genotype	Geographic distribution
A	Western Europe, North America and certain parts of Africa
B	Far East (China and Japan) and South East Asia
C	Far East (China and Japan) and South East Asia
D	Indian subcontinent, in the Middle East, the Mediterranean basin and some parts of Africa
E	West Africa and other parts of Africa
F	Central and South America as well as Polynesia

core, polymerase, and X proteins. Viral capsid containing double-stranded DNA traffic either to the nucleus, where it amplifies the viral genome, or to the endoplasmic reticulum, where the capsid engages the viral envelope proteins, buds into the lumen, and exits the cell as a virion that can infect other cells [18, 19].

Hepatitis B virus evades the innate response (which has an important role in limiting the spread of the pathogen) but appears to employ active evasion strategies that target the adaptive immune response, which is responsible for the elimination of HBV infection [10, 18]. CD4 T cells, classically referred to as helper T cells, are robust producers of cytokines and are required for the efficient development of effector cytotoxic CD8 T-cells and antibody production by B-cells. CD8 T cells go on to clear HBV-infected hepatocytes through cytolytic and noncytolytic mechanisms, reducing the levels of circulating virus, while the antibodies produced by B-cells neutralize free viral particles and can prevent (re)infection [10]. Another evidence that support the important role of the adaptive immunity is the significant overrepresentation of certain HLA class II alleles in patients with self-limiting disease course compared to patients who develop chronic disease [20]. Moreover, infected patients that become chronic carriers are characterized by absent, weak, or narrowly focused CD4 and CD8 T-cell responses to the corresponding viral antigens. The responsible mechanisms are not entirely clear, but T-cell deletion, anergy, exhaustion, and ignorance have all been reported to occur in chronic HBV-infected humans and chimpanzees [18].

T cell responses are responsible for the liver injury during acute and chronic phases of viral hepatitis. HBV-specific CD8+ T cells function as a double-edged sword. First, they play a critical role in the control and clearance of the viruses. Second, when overall antiviral immunity is not vigorous enough to clear virus, they may also induce sustained liver tissue damage through different pathways including perforin-mediated cytotoxicity and Fas ligand/Fas-mediated apoptosis [20].

Autoreactivity might also contribute to liver damage in chronic HBV infectious patients that present histological features of chronic active hepatitis (portal and periportal lymphoplasmacytic infiltrate and piecemeal necrosis of periportal hepatocytes). As HBV-infected cells are not predominantly concentrated in the periportal areas of the liver lobules, it is unlikely that a virus-directed T-cell cytotoxic reaction alone can account for this histological picture. Similar histological features are seen in autoimmune hepatitis, in which the hepatocyte-specific asialoglycoprotein receptor (ASGP-R) has been shown to be a major target of humoral and cellular autoreactions. In one study, it was found that 31 of 42 (73.8%) chronic HB patients with histological features of chronic active hepatitis (CAH) had antibodies against ASGP-R. The very marked association of anti-ASGP-R antibodies with moderate and severe CAH suggests that these antibodies are in some way related to the development of liver damage in HBV infectious patients and not simply the response to tissue damage [21]. Hence, liver cell damage that results from hepatitis B virus is both a consequence of the host's immune response to virus-infected hepatocytes (noncytopathyic effect of the virus) [1, 22] or secondary to viral induced apoptosis [12]. In both cases, as a result of the damage, autoimmune response may occur [22].

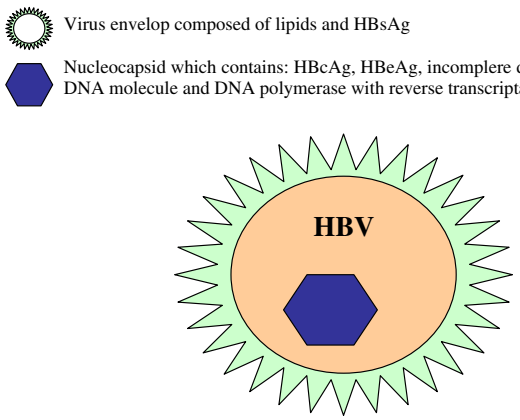

Fig. 1 Structure of hepatitis B virus

Clinical Course

The clinical course of hepatitis B infection is classified into four stages of varying duration. Stage 1 represents active viral replication and immune system tolerance. Stage 2 represents the development of a sufficient immunologic response to cause inflammation and subsequent hepatic tissue injury, including symptomatic hepatitis (asymptomatic inflammatory infection is possible but uncommon). By stage 3, clearance of virus-infected cells occurs and the viral component hepatitis B e antigen (HBeAg) is cleared, but not hepatitis B surface antigen (HBsAg). In stage 4, full immunity to HB has developed, and HBsAg is cleared.

Table 3 HBV serologic markers

Serologic marker	Significance	Population	Time course and population
HBsAg	Plays a role in the diagnosis of HBV infection [12]. It is one of the first serologic markers to become detectable in persons with acute HBV infection [9]	Chronic, Acute	Appears from the onset of the disease and eliminates from the blood when a persons recover from HBV infection [9]
HBsAb	Neutralizing antibodies that play a key role in recovery from HBV infection by containing the spread of infection in the infected host and facilitating the removal and destruction of viral particles. They also prevent reinfection by blocking the ability of virus particles binding to receptors on target cells [9, 11]	Recovered, immunized	Develop during convalescence in persons who recover from infection. Usually last for life but can become undetectable in some over time [9]
HBcAb	One of the first serologic markers to become detectable in persons with acute HBV infection [9]. Unable to neutralize viral infectivity [11]. They are not protective antibodies and their presence cannot be used to distinguish acute from chronic infection [15]	All patients who have exposed to HBV. Chronic, acute, recovered	Becomes detectable from the onset of the disease and persist for life in both persons with chronic infection and persons who recovered from the infection [9]
HBeAg	Although it has no known role in the viral life cycle, it may function as an HBV-specific immunosuppressive factor that protects the virus against immune attack; thus, it could be considered as a seromarker for high viral replication activity which correlates with greater infectivity [9, 12, 18]	Chronic, Acute	Present in the early phases of illness. For many persons with chronic infection, it becomes undetectable at some point after the acute infection [9]
HBeAb	Indicates lack of active viral replication [15]. These Ab are unable to neutralize viral infectivity [11]		Appear once the antigen has been cleared [15]
HBx protein	Plays an important role as a potent transactivator of cellular and viral genes that is required for initiation of infection [12]. Has an enhancing effect on intrahepatic purine and pyrimidine metabolism, which is required for efficient replication of HBV. It can also inhibit cellular proteasome activity when it is overexpressed. Thus, the HBx protein has the potential to inhibit antigen processing [18]		

HbsAg hepatitis B surface antigen, *HBsAb* hepatitis B surface antibody, *HBcAb* hepatitis B core antibody, *HBeAg* hepatitis B e antigen, *HBeAb* hepatitis B e antibody, *HBx protein* hepatitis B x protein

Persons whose infection does not progress beyond stage 1 or 2 are chronic carriers of hepatitis B [15].

Putative Mechanisms for the Induction of Autoimmunity by Viruses

It is likely that there is more than a single mechanism responsible for viral induced autoimmunity [4, 23]. Activation of autoreactive T cells is required for the induction of autoimmunity. Resting autoreactive T cells are part of the normal cell repertoire and do not induce disease. In experimental models of autoimmunity, disease can be transferred by activated, but not resting, auto-reactive T cells. Infectious agents have long been considered as culprits in the activation of such autoreactive T cells [24]. There has been considerable discussion regarding these points with respect to not only vaccination, but also transplantation, other aspects of autoimmunity and genetic predisposition [25–36].

The risk of T-cell-mediated autoimmunity is reduced by three main mechanisms: strongly self-reactive T cells are depleted in the thymus (negative selection), potentially autoreactive T cells are rendered anergic in peripheral tissues, and autoreactive T cells are silenced by regulatory T cells. However, despite these mechanisms, the tolerance for self proteins is breakable in genetically predisposed individuals [37] by the following mechanisms: molecular mimicry, epitope spreading, epitope modification, viral or bacterial superantigens, release of autoantigens during inflammation, bystander activation and/or dysregulation of the production of cytokines such as tumor necrosis factor alpha [3–5, 23].

Table 4 lists the mechanisms known to be caused by viruses thus generating autoimmunity.

Molecular mimicry based on amino acid similarities shared by viral and self antigens has long been proposed as a pathogenic mechanism for autoimmune disease but documentation of this mechanism has been elusive in humans because infection probably occurs years before the clinically overt autoimmune disease [3, 38]. Autoimmunity provoked by molecular mimicry should occur only when the viral and host determinants are similar enough to cross-react, yet different enough to break immunological tolerance. Moreover, the ability to find cross-reactive T-cells or antibodies that can recognize self-epitopes does not necessarily mean an autoimmune disease will develop [1]. The transition from cross-reactive immune responses to autoimmune disease depends on numerous intrinsic and extrinsic factors, such as the ability of the host histocompatibility complex (MHC) molecules to bind and present antigens, the likelihood of a peptide being processed for binding to the MHC, the presence in the periphery of B or T cells specific for self epitopes having escaped deletion and the level of cytokines induced after an immune recognition event [1, 3].

Epitope spreading is defined as the process in which specific antiviral responses in the early stages of infection become less sharply defined and extend to self antigens [39]. It is a phenomenon by which an exaggerated local activation of antigen presenting cells due to an inflammatory state results in enhanced processing and presentation of self antigens present at that site. Therefore, activation of a large number of T cells, including autoreactive T cells could lead to autoimmune disease [24].

Bystander effect is a process whereby the continued immune response to infection and attendant inflammation allows exposure of normally sequestered auto-antigens to the immune response [39]. This effect could be a consequence of the inflammatory response to the microbial agent that will result in cell destruction. Such cell destruction results from subsequent release of different cell ingredients, which will now be presented to the immune system at the inflammation site and result in an autoimmune disease [24, 40]. Another mechanism for the bystander effect is the significant activation of APCs caused by viruses. These activated APCs could potentially activate preprimed autoreactive T cells, which can then initiate autoimmune disease (bystander activation of autoreactive immune T cells) [3].

Microbial superantigens activate large numbers of T cells that express particular Vβ gene segments, and a subpopulation of these activated cells can be specific for a self-antigen [24].

Another mechanism suggested is the formation of immune complexes (IC) by viral antigens and antibodies generated against them. As a consequence, an immune response will develop to clear the complexes. A continuous antigen, antibody complexes could result in the development of autoimmunity. Moreover, infections could also lead to an autoimmune reaction associated with expression of MHC antigens on nonimmune cells. A local viral infection may cause production of gamma interferon or other inflammatory cytokines in the target organ, which in turn induce HLA class II expression, for the first time, in nonimmune cells. This can lead to presentation of autoantigens and activation of autoreactive T cells [41].

Table 4 Mechanisms by which an infector can contribute to the pathogenesis of an autoimmune disease

Mechanism	Description
Molecular mimicry	Shared immunologic epitope with a microbe and the host [3] thus a cross reactive immune response occurs both at the antibody and T cell level [23]
Epitope spreading	Specific anti-viral responses in the early stages of infection become less sharply define and extent to self antigens [39]
Bystander effect	Continued immune response to infection and attendant inflammation allows exposure of normally sequestered auto-antigens to the immune response [39]
Superantigens	Posses the ability to bind and activate a wide variety of T cells including the ones specific for a self-antigen [24]
Formation of immune complexes (IC)	Antigens produced by an infectious organism can form immune complexes with antibodies generated against them thus leading to an immune response that can result in the development of autoimmunity [41]
Expression of MHC antigens on non-immune cells	Virus can lead to an expression of HLA class II in non immune cells which can lead to presentation of autoantigens and activation of autoreactive T cells [41]
Direct inflammatory damage	Microbial agent causes an inflammatory response that may result in cell destruction and the subsequent release of cell ingredients that will be presented to the immune system for the first time, and lead to autoimmunity [24, 40]
Necrotic or apoptotic cells	Appearance of inaccessible target tissue that was not presented to the immune system will become available, and autoreactivity will occur [2, 12]

Another important mechanism is a direct inflammatory damage caused by the inflammatory response to the microbial agent, resulting in cell destruction and the subsequent release of different cell ingredients. These cellular ingredients will be presented to the immune system at the inflammation site and induce an immune response that may result in an autoimmune disease [24, 40].

It is important to keep in mind that these pathogenic mechanisms are not mutually exclusive and may be particularly relevant at different stages of disease development [24].

HBV and Autoimmune Diseases

Hepatitis B virus is associated with liver disease, but is also linked to extra hepatic manifestations, such as prodromal serum sickness in acute hepatitis, membranous glomerulonephritis, membranoproliferative glomerulonephritis, cutaneous vasculitis, infantile popular acrodermatitis, essential mixed cryoglobulinaemia, and polyarteritis nodosa (PAN), all forms of immune complex diseases. Furthermore, an association of HBV infection with other inflammatory syndromes has been suggested in diseases such as rheumatoid arthritis, polymyalgia rheumatica, and polymyositis [9, 42, 43].

These extra hepatic manifestations could be the result of the mechanisms leading to autoimmune phenomena, and thus supporting the theory that HBV is strongly associated with the development of autoimmunity. Therefore, we will review the association reported between HBV and autoimmune diseases.

HBV and Multiple Sclerosis

Multiple sclerosis (MS) is a white-matter demyelinating disease of the central nervous system (CNS) affecting young adults, characterized by perivascular CD4+ T cell and mononuclear cell infiltration, with subsequent primary demyelination of axonal tracks, leading to progressive paralysis [4]. The clinical course of MS in 85% of patients is relapsing–remitting, whereas in about 15% of patients, the disease presents as a primary progressive course. The disease is generally considered to involve an autoimmune pathology, with the presence of self-reactive lymphocytes targeting myelin peptides, such as myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG), leading to inflammation and myelin destruction within the brain and spinal cord. In addition to a genetic component, epidemiological studies provide strong circumstantial evidence for an environmental trigger, most likely viral, in the induction of MS, with the caveat that no virus has been consistently isolated from MS lesions [4, 40].

In humans infected with HBV, the body usually generates antibodies toward HBV antigens, but it is also possible that immunity against other components of HBV, such as DNA polymerase, will occur. Moreover, immunity to HBsAg may possess the potential of inducing CNS demyelination as there have been reports in several patients where HB vaccination using plasma-derived HBsAg was followed by optic neuritis, monophasic transverse myelitis, or demyelinating disease of the CNS [44].

HBV-DNA polymerase shares six consecutive amino acids with the encephalitogenic site of rabbit MBP. The rabbits were given injection of the HBV-DNA polymerase peptide that contained the six shared amino acids. The animals then developed antibodies and T cell reactivity that reacted both with the HBV-DNA polymerase and the native MBP. In addition, CNS specimens obtained from these rabbits had a histological picture reminiscent of the animal model of MS-experimental autoimmune encephalomyelitis (EAE). This study provides the first experimental evidence and strong proof of principle that viral infection may promote cross reactivity with self proteins through a molecular mimicry mechanism and, in the process, lead to tissue damage [1, 24].

Matsui et al. [44] described a 46 year old man with an extremely high titer of HBsAg and had experienced three attacks of acute demyelinating transverse myelitis associated with signs of meningeal irritation. Each episode showed a good response to corticosteroid therapy, and the circulating immune complexes were composed of HBsAg disappeared after treatment. This case suggests further that in some patients, HBV plays a role in demyelinative lesions.

HBV and Antiphospholipid Syndrome

Antiphospohlipid Syndrome (APS) is a multisystem disorder of an autoimmune origin characterized by recurrent arterial or venous thrombosis, pregnancy loss, and thrombocytopenia. It is also associated with the presence of antiphospholipid antibodies, which are a heterogeneous family of autoantibodies against negatively charged phospholipids thought to play a role in these clinical manifestations. The antiphospholipid antibodies include anticardiolipin (aCL) and lupus anticoagulant (LAC) antibodies [45–48].

Although APS are termed antiphospholipids, they do not bind directly to phospholipids but require the presence of certain plasma proteins (i.e. β_2GPI, prothrombin, annexin V, etc.) for optimal phospholipids binding activity. β2-glycoprotein I (β_2GPI), a phospholipids-binding protein, is

now recognized as the most clinically relevant antigenic target for antiphospholipid antibodies [39, 48].

The aCL antibodies are not found only in different autoimmune diseases but also in other conditions such as viral infection [39]. Several groups have reported that the aCL antibodies in autoimmune diseases must bind serum proteins such as β_2GPI to bind to cardiolipin (β_2GPI dependent), whereas this requirement is not found in the binding that occurs in association with various infections where they bind directly to phospholipids (β_2GPI independent). β_2GPI-dependent (pathogenic) antibodies seem to correlate with APS manifestations. Moreover, infection-induced aCL antibodies tend to be transient, of low titer, and more often of the IgM isotype, while autoimmune aCL antibodies often have highly sustained rather than transient titres, and are more often of the IgG isotype [46, 49].

In chronic liver diseases, prolonged damage to hepatic tissue may enable various macromolecules or phospholipids to enter the bloodstream, leading to the formation of complexes of various proteins and phospholipids. Such complexes could stimulate the synthesis of anticardiolipin antibodies [47].

In addition, it has been proposed that the molecular mimicry mechanism between infectious agents and the β_2GPI molecule may generate anti-β_2GPI antibodies [48]. The cell receptors for the lipid components of the HBV envelope include both annexin V and β_2GPI, which may act as a trigger mechanism to a possible aCL response [49].

Therefore, it could be speculated that HBV patients will generate antiphospholipid antibodies. In this respect, the data of Zachou et al. [46] are relevant. Zachou et al. searched for the presence of the IgG isotype of anti-cardiolipins (aCLs) antibodies and antibodies against β2-glycoprotein I (β2-GPI) in 50 patients infected with HBV. The results showed that 14% of HBV patients tested positive for IgG aCL antibody, which was significantly higher compared with healthy controls ($p<0.0001$), but only 2% of the HBV patients tested positive for anti-β2-GPIAbs. They concluded that low to medium titres of aCL antibodies are frequently detected in HBV patients. However, aCLs appear to be of the non-pathogenic type, as β2-GPI dependency was not revealed in the present study.

Guglielmone et al. [49] report in their study the occurrence of β2-GP I-dependent and β2-GP I-independent aCL isotypes in a number of patients with various infections, including HBV. It was found that 17 out of 40 patients with acute and chronic HBV (42%) were positive for aCL, and that the most prevalent isotypes in this population was IgM and IgA. The mean titre of the cofactor dependent was low in all groups. Another finding was that no correlation between disease activity (acute or chronic hepatitis B) and increased aCL levels. The authors concluded that aCL antibodies in patients with HBV are primarily cofactor independent. We should note, however, that in contrast, Harada et al. [47] have shown that anticardiolipin antibodies were rarely positive in patients with chronic HBV infection.

HBV and Autoimmune Thyroid Diseases

The autoimmune thyroid diseases (AITD) include a number of conditions that share common cellular and humoral immune responses targeted at the thyroid gland. The AITD include Graves' disease (GD) and Hashimoto's thyroiditis (HT), both of which involve infiltration of the thyroid by T and B cells reactive with thyroid antigens, production of thyroid autoantibodies, with the resultant clinical manifestations (hyperthyroidism in GD and hypothyroidism in HT) [41]. The main target autoantigen in autoimmune hypothyroidism is the cell surface protein thyroid peroxidase (TPO). The main target autoantigen in hyperthyroidism is the thyrotrophin receptor (TSHR), a G protein with seven membrane-spanning segments [39].

It is believed that the AITD are complex diseases in which susceptibility genes and environmental triggers act in concert to initiate the autoimmune response to the thyroid. The relationship between hepatitis B and HT has been investigated since both occur frequently in patients with Down's syndrome. In one study, it was found that a threefold increase in frequency of HT in patients with Down's syndrome who were carriers of HBsAg compared to patients with Down's syndrome and HBsAg negative [41].

Another association between HBV and thyroid diseases was found by Kansu et al. [50]. They have detected antibodies toward the tyroperoxidase (TPO) and thyroglobulin (Tg) in patients with HBV, but only after they have received interferon α (INF-α) treatment. These findings were not surprising since thyroid autoimmunity and/or dysfunction are the major autoimmune side effects of INF therapy for chronic viral hepatitis. Asymptomatic increases of preexisting thyroid autoantibodies or de novo induction of these autoantibodies have also been observed [51]. It is still not clear whether these autoantibodies are related to HBV or are only an intrinsic component of INF-α therapy. Thus, as can be seen from these data, HBV alone has not been found to be associated with an increase incidence of thyroid autoimmunity.

Rheumatic Diseases

Although several studies suggested that chronic HBV infection may act as a trigger for the development of autoimmune rheumatic diseases [8, 22], Permin et al. [43]

showed otherwise. They performed a study that investigated the presence of serological markers of HBV infection in 239 patients with different rheumatic diseases and checked for the presence of HBsAg, HBsAb, HBeAg, HBeAb. Those antigens and antibodies were determined by solid-phase radioimmunoassay, but only patients positive for HBsAg were investigated for HBeAg and HBeAb. The conclusion from that study was that HBV is not an etiological factor in rheumatic diseases except in some cases of polyarteritis nodosa (PAN).

HBV and Rheumatoid Arthritis

Rheumatoid arthritis is a systemic chronic inflammatory autoimmune disease characterized by symmetric inflammation and destruction of joints [52, 53]. The etiology of RA remains elusive, although it appears that genetic, infectious, environmental, and hormonal factors are all involved in complex interrelated ways [52].

Viruses are recognized as an important cause of arthritis, but their roles as causative agents of RA are not yet fully clear. It has been suggested that viruses targeting the cells of innate immunity can lead to the secretion of interleukin6 (IL-6) and tumor necrosis factor α (TNF-α) that are found to be important in the induction and maintenance of RA. Viruses could also target cells of adaptive immunity, inducing polyclonal activation of B cells and production of autoantibodies such as rheumatoid factor (RF) that are found in patients with RA. The autoantibodies could also be produced by molecular mimicry [37].

There is some evidence suggesting a pathologic link between HBV and RA [13, 54]. Patients with chronic hepatitis B virus may have arthralgia or arthritis similar to rheumatoid arthritis (RA) [37, 54].

Patients with RA generally are positive for both rheumatoid factor (RF) and antibody to cyclic citrullinated peptide (anti-CCP). Patients with chronic HBV may contain RF (especially the IgA isotype) in 20–75% of the cases but rarely do they contain anti-CCP. Therefore, even in the presence of RF, arthralgia or arthritis related with chronic hepatits B, patients do not develop or suffer from RA [54].

HBV and SLE

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune, connective-tissue disorder with a broad rage of clinical presentations [55]. SLE is characterized by an autoantibody response to nuclear and cytoplasmic antigens that include: dsDNA, histones, ribonucleoproteins, such as Ro60, LA, Ro52, and snRNP particle components, such as Sm proteins and A-RNP, ribosomal proteins, such as Ku and Su, and other cellular antigens. In patients, the autoantibody response is associated with inflammatory cascades and end-organ damage in kidney, skin, brain, lung, heart, and other organs [56]. The pathogenesis of SLE remains unclear, although the notion of apoptosis goes some way to explain how the immune system might recognize predominantly intracellular Ag. Autoantigens are released by both necrotic and apoptotic cells. Defects in the clearance of apoptotic cells have been described in this disorder and these defects could lead to aberrant uptake by macrophages, which then present the previously intracellular antigens to T and B cells, thus driving the autoimmune process [55].

Multiple factors including environmental, genetic, and immunological alterations are suspected in the development of SLE. One of the postulated mechanisms for the induction of disease is molecular mimicry where a microbial pathogen may be the inciting agent in the development of autoantibodies [57].

The suggestion that viruses may have a role in SLE is not new. Many extrahepatic manifestations are recognized in patients with HBV, including glomerulonephoritis, arthritis, vasculitis, and cryoglobulinaemia, features which are also frequently seen in SLE patients. It is possible that the HBV induces the lupus syndrome in susceptible individuals [58].

Lai et al. [59] aimed to clarify the possible pathogenetic role of HBV in SLE. In a 24-month period, renal biopsies were performed in 45 Chinese patients with SLE based upon the evidence of renal involvement. The HBV carrier status was routinely screened. HBsAg and its antibody (HBsAb) were determined by reversed passive hemagglutination and antibodies to hepatitis B core antigen (HBcAg) by immune adherence hemagglutination. Percutaneous renal biopsy was performed and the renal biopsy specimens were processed for light microscopy, immunoflurescence, and electron microscopy studies. Using the immunoflurosecence studies, their group failed to demonstrate high incidences of HBsAg or HBcAg in the glomerular immune complex deposits of patients with SLE alone. The conclusion of this study was that there is no increased prevalence of HBsAg in sera or kidney among patients with SLE. Moreover, it was found that the prevalence of HBsAg carrier in their patients with SLE was not significantly different from that of the general population of Hong Kong.

Ziegenfuss et al. [60] however, have found HBsAg in sera of patients with SLE, but only after the sera had been treated with 0.04 M mercaptoethanol that is used to break down RF, which had previously been shown to be capable of masking HBsAg. Additionally, they suggested heating (56°C for 30 min) sera in assays for HBsAg because certain sera contain a heat-labile factor (probably Clq^5) that can mask HBsAg and agglutinate latex particles just as rheumatoid factor does.

Based on evidence of the presence of HBsAg in glomerular immune complexes in patients with renal disease of varying morphological patterns, including membranous, proliferative and mesangiocapillary glomerulonephritis and focal glomerulosclerosis, Looi et al. [58] aimed to find the frequency of HBsAg immune deposits in lupus nephritis. Over a 3-year period, they examined renal tissue from 259 patients, including 47 with SLE. They revealed 43 cases with HBsAg in glomerular immune complexes and a significantly high proportion of these were SLE patients: 64% of SLE patients with renal immunofluorescence examination also exhibited fluorescent glomerular deposits of HBsAg compared to 4% in the non-SLE group ($p<0.001$). In all cases, the fluorescent HBsAg deposits were granular in nature and located in the glomerular capillary walls. They concluded that a high prevalence of HBsAg was found in glomerular immune complexes of lupus nephritis patients. HBsAg was found only rarely in glomerular immune complexes associated with other forms of glomerular disease. Nonetheless, it is possible that HBsAg-Ab complexes tend to localize in the glomeruli of SLE patients more readily than non-SLE patients, due either to nonspecific binding by damaged glomeruli, trapping by immune complex deposits of other specifications, or related to the concentration of HBsAg by cryoprecipitates deposited in the glomeruli [58].

Autoantibodies to proliferating cell nuclear antigen (PCNA) are detected in 3–5% of sera in patients with systemic lupus erythematosus (SLE). These antibodies are not detected in other autoimmune diseases and are thought to be a specific and useful serological marker for SLE [22]. In a study performed by Tzang et al. [22], the prevalence of anti-PCNA in 243 chronic HBV patients was about 12%. The isotype distribution of anti-PCNA was predominantly IgG (80%) and a minority of IgM (20%). These are similar results to spontaneously arising autoantibodies in SLE, which are predominantly IgG with a low level of IgM. Moreover, none of these patients exhibit clinical manifestations of SLE. It is still unknown how long this antibody will persist in patients with chronic HBV [8] and, if in the long run, these patients would develop manifestations of SLE.

HBV and Glomerulonephritis

Glomerulonephritis is characterized by intraglomerular inflammation and cellular proliferation associated with hematuria [61].

Several observations suggest that the hepatitis B virus might be involved in the pathogenesis of some forms of glomerulonephritis. Deposits of HBsAg within the glomeruli along with immunoglobulins and complement factors have been detected occasionally in patients with glomerulonephritis. Moreover, circumstantial evidence suggests that HBsAg immune complexes play a pathogenic role in the glomerulonephritis associated to essential mixed cryoglobulinemia (EMC) [62]. Animal experiments and observations on human subjects have demonstrated that HBV-containing immune complexes may be formed in the course of acute and chronic HBV infection. Immune-complex glomerulonephritis has been reproduced in an experimental model by inoculation of baboons with human HBsAg, and immune complex glomerulonephritis has been demonstrated in patients with acute hepatitis B infection. The high prevalence (20%) of HBs antigenaemia in south African Bantus with chronic glomerulonephritis has been interpreted to indicate that HBsAg immune complexes are involved in the pathogenesis of glomerlonephritis [63]. Membranous nephropathy (MN) is generally regarded as a typical example of an immune complex disease of either idiopathic origin or the consequence of other mechanisms such as infectious diseases or of autoimmune origin. HBsAg has been demonstrated to be associated with several different types of glomerulonephritis and especially MN [64].

Maggiore et al. [62] support these suggestions of the pathogenic relationship between the HBV infection and glomerulonephritis. They screened 136 consecutive patients with various types of glomerular lesions for the presence of HBsAg, either in serum or in kidney biopsy specimens by means of radioimmunoassay and direct immunofluorescence and found that 11 (8%) had HBs antigenemia. In the general hospitalized population of Southern Italy, it is only 2.7%.

Lai et al. [63] defined HBV-associated glomerulonephritides as a primary glomerular disease with the persistent presence of HBsAg in sera before and after renal biopsy. Glomerular deposits of immune complexes containing HBsAg and/or HBcAg were detected in 41, 61, and 60% of membranous nephropathy, IgA nephropathy, and mesangial proliferative glomerulonephritis associated with persistent HBs antigenaemia, respectively. Finally, in a study by Hsu et al. [64], 13 children with membranous nephropathy (MN), that was not associated with SLE, were found to be sera positive for the presence of HBsAg and anti-HBc.

Vasculitis

The vasculitides are a heterogeneous group of disorders characterized by inflammation of blood vessels and classified to three groups depending on the size of the involved vessels [65, 66]. The etiology of the disease is generally unknown. The possibility of an infectious cause has prompted a variety of reports suggesting, but not proving, a causal relationship between infectious agents and vasculitis. The best known association is that of HBV with polyarteritis nodosa (PAN). Two mechanisms for

infection-associated vasculitis have been proposed, direct microbial toxic damage to the vascular wall has been distinguished from immune mediated damage by a humoral or cellular mechanism [65].

Infectious agents in general and viruses in particular can be the underlying cause of several vasculitides, usually of small- or medium-sized vessels and do not seem to be associated with antineutrophil cytoplasmic antibodies (ANCA) [67, 68]. Recognizing an infectious origin of vasculitides is of a great importance because treatment strategies differ from those applied to noninfectious forms [68]. Approximately 30% of patients with systemic vasculitis have been found to have HBsAg in the vessel wall [69]. Two major vasculitides can occur as a consequence of viral infection: classic polyarteritis nodosa, as a result of HBV infection, and mixed cryoglobulinemia, in patients infected with HCV [67, 68, 70], but it is also possible for HBV to be related to cryoglobulinemia; there is a 50% prevalence of HBV in mixed cryoglobulinemia [65].

HBV and Polyarteritis Nodosa

Polyarteritis nodosa is a systemic necrotizing vasculitis predominantly involving medium-sized vessels. The vascular lesions of PAN are typically segmental and tend to involve the bifurifications and branchings of the arteries, occasionally spreading to the adjacent veins. Inflammation occurs followed by fibrinoid necrosis of the involved vessels with luminal compromise, thrombosis, and infarction in some cases of hemorrhage [69]. The main manifestations are subacute weight loss, fever, and asthenia, peripheral neuropathy, renal involvement, musculoskeletal and cutaneous involvement, hypertension, gastrointestinal (GI) tract involvement, and cardiac failure. The vascular inflammation arises most commonly through an immune complex (IC)-induced mechanism [71]. Circulating immune complexes (CIC) composed of HBsAg and immunoglobulin have been detected in patients with PAN [69].

During the 1970s, about half of the patients with classic PAN were infected with HBV. However, over the past few years, the frequency of HBV-PAN has declined from 35% in 1984 to less than 5% today [68]. Approximately 30% of patients with systemic vasculitis and up to 50% of patients with polyarteritis nodosa, have been found to have HBsAg in the vessel wall [69]. Thus, HBV has been considered to be a cause of PAN. The detection of HBsAg and HBV DNA particles using highly sensitive techniques increased the prevalence of HBV-related PAN to 75%. This finding strongly supports a causal relationship between HBV and the disease [65]. Moreover, there is evidence of IC disease with hepatitis B antigen being the triggering antigen causing the disease [71].

HBV-associated PAN is a typical form of classic PAN [72] and usually becomes manifest less than 12 months after viral infection [68]. It is typically a macroscopic (or classical) form of PAN, with renal vasculitis and numerous microaneurysms associated with a high level of viral replication without rapidly progressive glomerulonephritis and without antineutrophil cytoplasmic antibodies (ANCA)-mediated vasculitis [71]. Hepatitis is rarely diagnosed, as it is usually silent before PAN develops and remains absent or mild when PAN symptoms appear. Immune complex deposition on and throughout vessel walls, in an excess amount of viral antigens, could trigger vasculitis and be responsible for subsequent organ damage. Clinical manifestations start suddenly and are roughly the same as those commonly observed in PAN. Orchitis, gastrointestinal and kidney vessel involvement, with hypertension, are common in HBV-PAN, whereas cutaneous and pulmonary symptoms are rare. Once remission has been obtained, HBV-PAN tends not to recur [68].

Guillevin et al. [72] observed 341 cases of PAN in patients between the years 1972–2002, the etiology of 115 (33.7%) of those patients was due to HBV. Permin et al. [43] found an increased prevalence of HBsAg in patients with PAN. Furthermore these patients were all HBeAg-positive at the onset of their disease, indicating an active viral replication. Few patients had an onset of PAN with a biopsy-verified acute hepatitis, and in one patient, the delay between onset of the hepatitis and onset of PAN might indicate that the PAN was triggered by the HBV infection.

HBV-related PAN was investigated by Guillevin et al. [71] who evaluated 41 patients with HBV-related PAN and found that the immunologic process responsible for PAN occurs early in the course of HBV infection. In most cases, when the HBV contamination could be dated, PAN developed less than 6 months after infection. Hepatitis was diagnosed occasionally, but was silent in most cases, with PAN being the first manifestation of HBV infection. They have also shown that in this group of patients, clinical data were roughly the same as those commonly observed in patients with PAN. The differences found: malignant hypertension, renal infarction, and orchiepididymitis were more often associated with HBV infection. Rapidly progressive glomerulonephritis, as in microscopic polyangitis, was not observed in patients with HBV-related PAN. Moreover, only one patient was found to be ANCA-positive in the immunofluorescence assay which can point to the conclusion that HBV-related PAN is not an ANCA-related disease and that other immunologic mechanisms are probably involved.

Trepo et al. [73] investigated the role of hepatitis HBsAg and specific immune complexes in polyarteritis. For that purpose, sera from 55 histologically confirmed cases were tested for the presence of hepatitis B antigen-associated particles and HBsAb by solid phase radioimmunoassay,

electron microscopy, and passive haemagglutination. Later on, they showed the presence of HBcAb in almost all the cases with either HBsAg and/or HBsAb. Those findings confirm actual or recent replication of hepatitis B virus in the cases above. It was concluded from their study that circulating hepatitis B antigen antibody complexes may be responsible for vasculitis or polyarteritis, but do not appear to be pathogenic for the liver.

HBV and Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is characterized by fluctuating alanine aminotransferase (ALT) levels in serum, marked hyper-gammaglobulinemia and circulating organ and non-organ specific autoantibodies. It is uncommon with a female predominance, although a genetic predisposition has been suggested [74, 75]; prevalence varies but is around 0.01–0.02%. AIH is characterized serologically by a striking increase in serum IgG. The natural course is marked by recurrent necro-inflammatory episodes within the liver lobules and at the interface with the portal tracts eventually leading to cirrhosis and possibly liver failure. Autoimmune hepatitis is divided into two main forms, types 1 and 2; the former is characterized by high titer autoantibodies to nuclei (ANA) reactive with chromatin and occasionally dsDNA and/or antibodies to substrates of smooth muscle (SMA) reactive with F-actin microfilaments. Type 2 is overall rare (20 times less frequent than type 1) but usually occurs in younger patients and with typical type 1 antibodies to liver/kidney microsomes (LKM1) directed against the cytochrome P450 isoform 2D6 [76].

If indeed a trigger is required to set off a sequence of events leading to autoimmune hepatitis type 1 in a predisposed individual, viruses are among the most likely candidates. Two case reports have linked hepatitis B virus infection to AIH type 1: the first case followed acute HBV infection in a young woman who had eliminated the virus. The second developed in a chronic HBV carrier concurrently with the emergence of mutant, HBeAg-negative virus and was directly related to viral multiplication, as the disease went into remission after inhibition of HBV replication [76]. Murakami et al. [74] described a case report of a 43-year old Japanese woman who was diagnosed as having AIH 10 years after HBV infection. The diagnosis was based on the following: in the time course between testing positive for HBsAg and the onset of AIH, she remained an asymptomatic HBV carrier with normal liver function. Ten years later, this woman was hospitalized and elevated serum level of ALT was observed. It was also found that her human leukocyte antigen (HLA) typing is DR4 which is strongly associated with autoimmune hepatitis in Japanese patients. Based on biochemical, serological, histological, and immunohistochemical results, the authors diagnosed the mechanism of liver damage in this patient to be autoimmune rather than HBV-induced. Her good response to immunosuppressive therapy supported the role of an autoimmune mechanism. On the other hand, Czaja et al. [75] assessed the possibility of a viral cause of autoimmune hepatitis by screening well-characterized patients for serologic markers of hepatitis B and C virus infection and found that patients with severe autoimmune hepatitis typically lack serologic markers of viral infection and have a distinctly different clinical, immunoserologic and HLA phenotype than counterparts with viral chronic active hepatitis (CAH).

HBV and Type 1 Diabetes

Type 1 diabetes (T1D) results from the destruction of pancreatic beta cells, and genetic and environmental factors are believed to be a major component for the development of disease. Viruses have long been suspected to contribute to the onset of T1D in at least two distinct ways. Virus may trigger beta cell-specific autoimmunity leading to diabetes, or may directly infect and destroy insulin-producing pancreatic beta cells, resulting in clinical T1D [77].

Khuri et al. [78] aimed to assess the relationship between hepatitis B virus markers and diabetes mellitus. Essentially, serum markers for HBV were studied in 395 healthy control subjects and 100 diabetic patients. The HBV markers tested included HBsAg, HBsAb, and HBcAb. HBe antigen and antibody were measured in those patients who were HBsAg-positive. The control population was tested only for HBsAg and HBsAb. Compared with a control population, the diabetic subjects showed a significantly higher prevalence of HBV markers. Despite these results, this study cannot determine whether onset of diabetes preceded the HBV infection or vice versa. Halota et al. [79] demonstrated the serum presence of HBcAb in 123 of 315 patients suffering from T1D, and they suggested that patients suffering from T1D incur a high risk of infection with hepatotropic viruses because of frequent hospitalizations and blood tests and this is the reason for the high proportion of antibodies toward HBV found in patients with DM. Therefore, T1D is the cause of HBV and not the opposite.

HBV and Uveitis

Uveitis is an intraocular inflammatory disease which affects the uveal tract and the retina of the eye and is a major cause of visual impairment. Noninfectious uveitis is thought to be autoimmune in nature. The retinal soluble protein (S–Ag) has been implicated as a pathogenic protein for the induction of experimental autoimmune uveitis (EAU), and

Table 5 Various autoimmune diseases and the association with HBV infection

AID	Description	Findings related with HBV	Conclusions
MS	Self-reactive lymphocytes targeting myelin peptides, such as myelin basic protein (MBP), results in white-matter demyelinating disease of the CNS that lead to progressive paralysis [4]	(1) MS like syndromes following Hepatitis B (HB) vaccination using plasma-derived HBsAg [44]. (2) Molecular mimicry between HBV-DNA polymerase and MBP that leads in animal to EAE [1, 24]. (3) In one case high titer of HBsAg was found to correlate with acute demyelinating attacks [44]	A cause and effect relationship is yet to be proven
APS	Multisystem disorder characterized by recurrent arterial or venous thrombosis, pregnancy loss and thrombocytopenia. It is primarily associated with aCL antibodies that are β_2GPI dependent [39, 48]	(1) Prolonged damage to hepatic tissue may stimulate the synthesis of aCL antibodies [47]. (2) cell receptors for the lipid components of the HBV envelope include both annexin V and β_2GPI, which may act as a trigger mechanism to a possible aCL response [49]. (3) Zachou et al. [46] and Guglielmone et al. [49] showed high prevalence of aCL antibodies (mostly of β_2GPI independent, non pathogenic form) in HBV compared with normal control. (4) Harada et al. [47] have shown that Acl antibodies were rarely positive in patients with chronic HBV infection	Although low to medium titres of aCL antibodies are frequently detected in HBV patients, it seems that these Abs are not associated with APS since they are mostly the non-pathogenic type (β_2GPI independent)
RA	Systemic chronic disease characterized by symmetric inflammation and destruction of joints [52, 53]. In order to diagnose RA, patients need to test positive for both RF and antibody to cyclic citrullinated peptide CCP [54]	(1) Patients with chronic HBV may have arthralgia or arthritis similar to RA [37, 54]. (2) Patients with chronic HBV may contain RF in 20–75% of the cases but rarely do they contain anti-CCP [54]	Patients with HBV usually do not develop or suffer from RA despite arthralgia or arthritis symptoms and the presence of RF since the lack of CCP [54]
SLE	Multisystem, connective-tissue disorder with a broad rage of clinical presentations [55]. Characterized by an autoantibody response to nuclear and cytoplasmic antigens [56].	(1)Lai et al. [59] failed to demonstrate high incidences of HBsAg or HBcAg in the glomerular immune complex deposits of patients with SLE. (2) Ziegenfuss et al. [60] however, have found HbsAg in serum of patients with SLE, but only after breaking down RF, which had previously been shown to be capable of masking HBsAg. (3) Looi et al [58] have revealed high prevalence of HBsAg in glomerular immune complexes in lupus nephritis	Based on those controversy results, it is still unknown if there is a cause and effect relationship between HBV and SLE
GN	Disease involving the renal glomeruli and is characterized by intraglomerular inflammation and cellular proliferation associated with hematuria [61]	Deposits of HBsAg within the glomeruli along with immunoglobulins and complement factors have been detected occasionally in patients with GN. Moreover, HBsAg immune complexes are found to be involve in the pathogenesis of GN and especially MN [62–64]. Maggiore et al. [62] found 8% of GN patients had HBs antigenemia compared with 2.7% in the general hospitalized population of Southern Italy. Lai et al. [63] showed glomerular deposits of immune complexes containing HBsAg and/or HBcAg in 41, 61, and 60% of MN, IgA nephropathy	It seems as if HBV plays a role in the pathogenesis of GN

Table 5 (continued)

AID	Description	Findings related with HBV	Conclusions
		and mesangial proliferative glomerulonephritis, respectively	
PAN	Systemic necrotizing vasculitis predominantly involving medium-sized vessels [69]. The vascular inflammation arises most commonly through an immune complex (IC)-induced mechanism [71]	Circulating immune complexes (CIC) composed of HBsAg and immunoglobulin have been detected in patients with PAN [69]. There is evidence of IC disease with hepatitis B antigen being the triggering antigen causing the disease [71]. Guillevin et al. [72] demonstrated that the etiology of 33.7% of observed patients was due to HBV. Permin et al. [43] found an increased prevalence of HBsAg in patients with PAN Trepo et al. [73] concluded that circulating hepatitis B antigen antibody complexes may be responsible for vasculitis or polyarteritis	There is a causal relationship between HBV and PAN where HBV is considered to be a cause of the disease
AIH	Characterized by fluctuating alanine aminotransferase (ALT) levels in serum, marked hyper-gammaglobulinemia and circulating organ and nonorgan specific autoantibodies [74, 75]. Two types of AIH exists: type 1 associate with ANA and SMA where type 2 strongly correlate with LKM1 auto-antibodies [76]	Few case reports have linked HBV infection to AIH and especially to type 1 [74, 76]. On the other hand, Czaja et al. [75] found that patients with severe autoimmune hepatitis typically lack serologic markers of viral infection	There is not enough data to conclude the role of HBV infection in the pathogenesis of AIH
T1D	Disease due to the destruction of insulin-producing pancreatic beta cells [77]	Khuri et al. [78] demonstrated that compared with a control population, the diabetic subjects showed a significantly higher prevalence of HBV markers. Halota et al. [79] demonstrated serum presence of HBcAb in about 40% patients suffering from T1D	Based on these finding it can't be said whether the onset of T1D preceded the HBV infection or vice-versa
Uveitis	Intraocular inflammatory disease which affects the uveal tract and the retina of the eye and is a major cause of visual impairment [80]	HBV infection may sensitize mononuclear cells to cross-react with self proteins such as retinal S–Ag through a molecular mimicry mechanism [1]	Despite the insufficient data, HBV could be one of the triggers for Uveitis

AID autoimmune disease, *MS* multiple sclerosis, *APS* antiphospohlipid syndrome, *EAE* experimental autoimmune encephalomyelitis, *MBP* myelin basic protein, *aCL* anticardiolipin, β_2*GPI* β2-glycoprotein I, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *CCP* cyclic citrullinated peptide, *SLE* systemic lupus erythematosus, *GN* glomerulonephritis, *MN* membranous nephropathy, *PAN* polyarteritis nodosa, *AIH* autoimmune hepatitis, *ANA* antinuclear antibodies, *SMA* smooth muscle antibodies, *LKM1* liver/kidney microsomes type 1, *T1D* type 1 diabetes

two major uveito-pathogenic sites have been identified as part of its sequence: peptide G and peptide M [80].

In an animal study, it was found that HBV DNA polymerase shares amino acid sequence similarities with peptide M of retinal S–Ag. Moreover, it was found that the synthetic peptide, corresponding to the amino sequence of HBV DNA pol, containing five consecutive amino acids identical to peptide M in S–Ag induced EAU in Lewis rats. Mononuclear cells from monkeys immunized with peptide M also showed significant proliferation when incubated with either peptide M or the synthetic peptide as measured by in vitro lymphocyte proliferation. Histopathological findings in the monkey retina closely resemble those seen in human patients with uveitis. Based on these findings, it was concluded that HBV infection may sensitize mononuclear cells to cross-react with self proteins such as retinal S–Ag through a molecular mimicry mechanism [1]. Although there is not sufficient data, it seems as if HBV has a potential role as an environmental trigger for the development of uveitis but more data is needed.

HBV and INF-α Treatment

It is believed that INF-α, which is an effective treatment of chronic HBV infection, could be responsible for the

induction of autoimmune phenomena ranging from appearance of tissue autoantibodies to an overt autoimmune disease, such as thyroiditis, systemic lupus erythrmatosus, vasculitis, hemolytic anemia, thrombocytopenis and polyarthritis [81]. Therefore, the presence of autoantibodies after HBV infection could be the result of treatment with INF-α instead of an intrinsic component of HBV infection.

Kansu et al. [50] supported this theory. They evaluated the presence of auto-antibodies toward thyroid peroxidase (TPO), thyroglobulin (Tg), anti-nuclear (ANA), anti-dsDNA, anti-mitochondrial (AMA), smooth muscle (SMA) and liver kidney microsomal-1 (LKM-1) in 61 children with chronic HBV infection before and after treatment with INF-α. The authors found that autoantibody formation may occur in those children and that the autoantibody prevalence was highly affected by the use of INF. They did not detect anti-ds DNA Ab before or after the use of INF. Antibodies toward LKM-1, TPO, and Tg were detected only after the use of INF.

Not all agree with these findings. Gregorio et at [81], for example, studied whether any clinical or serological signs of autoimmune liver diseases are induced by INF-α treatment. They followed 61 children participating in a multicenter, randomized, controlled trial, including a group of untreated patients, for a median of 4 years, and analyzed the prevalence of tissue autoantibodies in 331 of their sera collected over this period. Their data revealed that a similar proportion of treated and untreated patients developed autoantibodies (mainly IgG isotype) at a similar titer, suggesting that autoantibody production is an intrinsic component of chronic HBV infection rather than a consequence of INF-α treatment. In addition, they showed that autoantibody prevalence and behavior over time is largely unaffected by the use of therapeutic doses of INF-α. Therefore, the presence of ANA, SMA, and to a lesser extent, GPC, is part of natural history of chronic liver disease caused by HBV infection, despite the use of INF-α as a treatment.

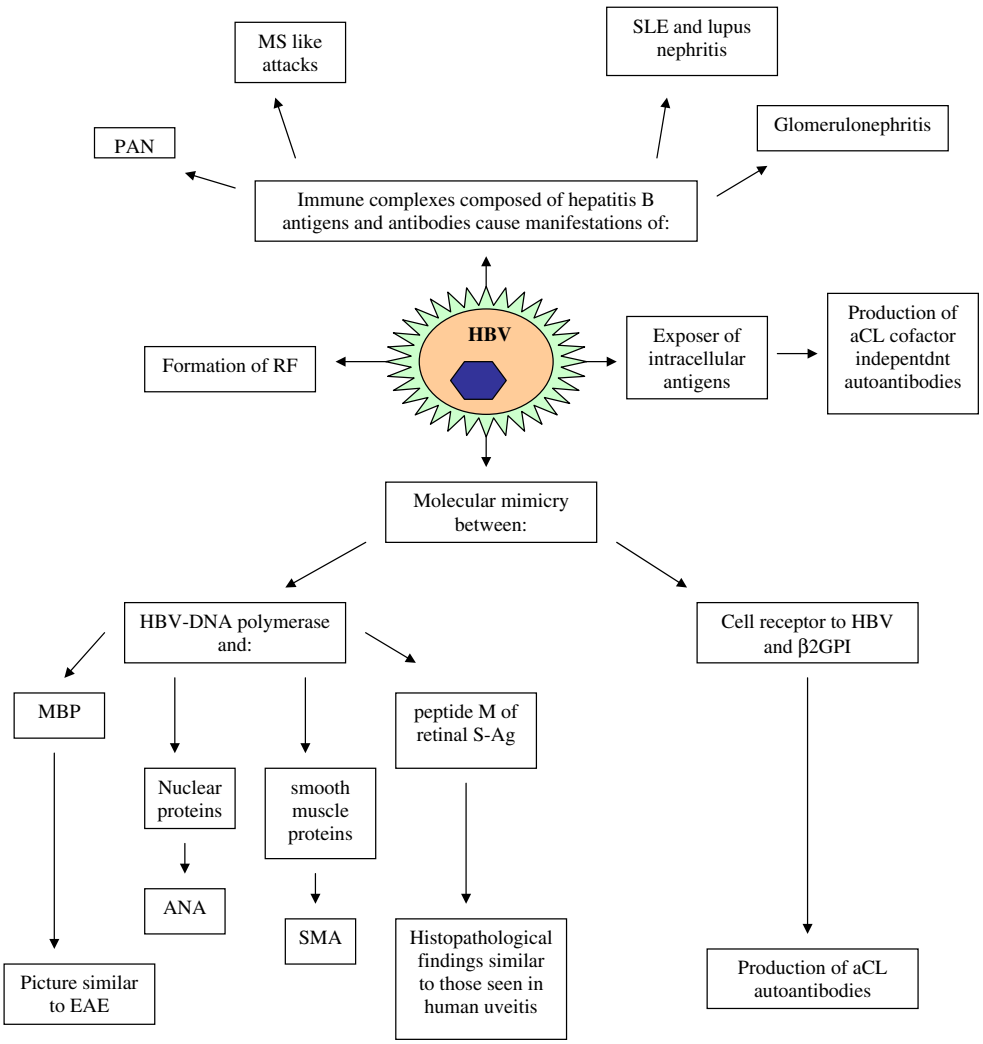

Fig. 2 Summary of the mechanisms leading to autoimmune phenomena in HBV

Gregorio et al. [82] also investigated the possibility that these autoantibodies could be produced by an inappropriate host immune response to viral antigens by molecular mimicry, a mechanism described widely above. They scanned protein databases to search for sequence similarities between HBV proteins and putative antigenic targets of ANA and SMA. Using a computer-assisted scanning protocol, they identified six human proteins that have high local sequence similarity with the HBV-DNA polymerase: four nuclear proteins and two smooth muscle proteins. The four nuclear proteins appear to be key proteins involved in structural and regulatory functions, whereas the smooth muscle proteins are involved in muscle contraction. After these findings, Vergani et al. [83] have shown that HBV-DNA polymerase shares seven to nine amino acid sequences with nuclear (MHCII transactivator, nuclear pore core protein, nuclear mitotic apparatus, polymyositis sclerosis antigen) and smooth muscle proteins (caldesmon, myosin).

Hepatitis B Vaccination and Autoimmunity

Genetically engineered hepatitis B vaccines were developed and licensed during the 1980s in the USA. These vaccines are most commonly produced by inserting the gene for the HBsAg into the yeast *Saccharomyces cerevisiae*. After growth of the yeast, vaccine is prepared by lysing the yeast to free HBsAg particles, which are separated from yeast components by biochemical and biophysical methods [84].

Distribution of the vaccine indeed lead to a dramatic reduction in HBV complications in countries that have implemented large-scale vaccination programs [85], but large series of autoimmune adverse events have been reported in the scientific literature after this vaccine [84, 86]. The autoimmune adverse events include: SLE, Guillain-Barre' syndrome, rheumatic disorders, uveitis, lichen rubber planus, nephritic syndrome, CNS demyelinization and relapsing MS [85, 87–89].

Hepatitis B vaccination could break self-tolerance and induce autoimmune adverse events by synergistic interaction between the immunological stimulatory components of the immunization (including: the HBsAg, aluminum adjuvant, mercury preservative and residual yeast proteins) in a genetically susceptible vaccine recipient, within fairly close temporal association with vaccine administration [84]. Several plausible mechanisms have been suggested. Molecular mimicry between the recombinant HBsAg and self proteins could be the answer for these effects. An increased expression of major MHC class II molecules by nonprofessional APCs, and the activation or dysregulation of T- and/or B-lymphocytes (such as autoreactive T cells) by vaccines or their adjuvants has been also proposed to explain the possible induction of autoimmune diseases by vaccines and other immunostimulating substances [86, 88].

It is important to keep in mind that despite these adverse events, the benefits of hepatitis B prevention by the vaccine far outweigh the risk of autoimmune diseases [86].

Conclusion

Taking into consideration the relevant data about the relationship between HBV and autoimmune diseases, it is clear that HBV and autoimmunity are somehow linked. Table 5 summarized the association known between HBV and autoimmune diseases, and Fig. 2 depicts the mechanisms by which HBV cause autoimmune manifestations. Several mechanisms have been linked to HBV as the inducer of some autoimmune phenomena. These include: molecular mimicry between HBV antigens and self proteins, the generation of immune complexes between HBV antigens and antibodies and apoptosis/tissue damage resulting in the exposure of intracellular antigens [1, 12, 24, 58, 63, 69]. Excluding the case in which HBV has been shown to induce PAN; all the other findings so far do not prove a cause and effect relationship between HBV and the development of autoimmune diseases. Thus, it could be suggested that autoimmune patients are more prone to be infected with HBV as suggested by Halota et al. [79] in the case of patients with type 1 diabetes mellitus. Some studies have detected the appearance of autoantibodies after HBV infection, but rarely do these patients suffer from the autoimmune disease related to the autoantibodies [1, 49, 54]. It should be noted that years may go by before an autoimmune disease develops. This point can be well illustrated in several other autoimmune diseases, which may reflect the relationships between the genetics of the host response and environmental agents [90–101]. Therefore, making an association between viral infection and the development of autoimmune disease may be a hard and elusive task.

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