

Autoantibodies in Hepatitis C Virus-Related Chronic Liver Disease

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Persistent hepatitis C virus (HCV) infection evokes autoimmune response including production of autoantibodies and concomitant autoimmune disorders. Numerous types of autoantibodies such as non-organ-specific autoantibodies and liver-specific autoantibodies have been identified in sera of patients with HCV-related chronic liver disease (CLD). The production of these autoantibodies in HCV-related CLD reflects "virus-induced autoimmunity." Molecular mimicry between the HCV polyprotein and self-proteins, and polyclonal B cell activation by chronic HCV infection have been proposed as possible mechanisms for the occurrence of autoantibodies in HCV-related CLD. Some autoantibodies are tightly associated with concurrent autoimmune diseases, and others closely associated with peculiar human leukocyte antigen (HLA) haplotypes. Changes in the titers of autoantibodies during the antiviral treatment may predict the sustained virological response in individuals. In this article, we mainly focus on the interpretations of autoantibodies in HCV-related CLD.

Keywords: Antiviral Treatment, Autoantibodies, Hepatitis C Virus, HLA Haplotype, Molecular Mimicry

Introduction

Autoantibodies were frequently found in patients with viral infections including Epstein-Bar (EB) virus ⁽¹⁾, measles virus, and herpes simplex virus ⁽²⁾ before the discovery of hepatitis C virus (HCV). Patients with infectious mononucleosis secondary to EB virus transiently had autoantibodies to cytoskeletal components, especially those to intermediate filaments, in their sera ⁽¹⁾. Viral infection appears to trigger the development of the autoantibodies. Therefore, the production of these autoantibodies in viral infection is regarded as virus-induced autoimmunity ⁽³⁾.

Chronic HCV infection frequently leads to autoimmune response including the production of autoantibodies and the coincidence of autoimmune diseases ^(4,5). The diversity of autoantibodies such as non-organ-specific autoantibodies and liver-specific autoantibodies has been widely established in sera of patients with HCV-related chronic liver disease (CLD) ⁽⁶⁻⁸⁾. Some autoantibodies in chronic HCV infection have biochemical, histological, or genetic characteristics, while other autoantibodies may predict the response to antiviral treatment, concomitant disorders, or prognosis in patients with

HCV-related CLD.

Herein, we would like to review different aspects of autoantibodies in HCV-related CLD and discuss their clinical and therapeutic implications in HCV-related CLD.

Autoantibodies observed in patients with HCV-related CLD

Close association of chronic HCV infection with the occurrence of autoantibodies has been widely described. Table 1 summarizes the autoantibodies that have been identified in HCV-related CLD so

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far. These autoantibodies are mainly divided into five groups: i) autoantibodies as serological markers for autoimmune liver disease; ii) autoantibodies as serological markers for extrahepatic autoimmune diseases; iii) autoantibodies to endocrine organs; iv) autoantibodies to tumor-associated antigens and v) other autoantibodies. Many investigators have revealed that the emergence of these autoantibodies are independent of HCV genotypes⁽⁹⁻¹²⁾. Among the autoantibodies listed in Table 1, antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) are the most common non-organ-specific autoantibodies (NOSA) in patients with HCV-related CLD. Parietal cell antibodies (PCA), and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) are also associated with HCV-related CLD. Autoantibodies to liver-kidney microsome type 1 (LKM1), liver cytosol type 1 (LC-1), soluble liver antigen (SLA), and asialoglycoprotein receptor (ASGPR), which correspond to the serological markers for autoimmune hepatitis (AIH), are rarely detected in HCV-related CLD. Autoantibodies to endocrine organs, including antibodies to islet cell (ICA), antibodies to glutamic acid decarboxylase (GAD), and antibodies to adrenal cortex, often emerge before and/or during the treatment with interferon (IFN) alone or IFN plus ribavirin.

As the serological hallmarks for concomitant autoimmune diseases, thyroid microsome autoantibodies (TMHA), thyroglobulin autoantibodies (TGHA), and antibodies to thyroid peroxidase autoantibodies (anti-TPO) are present in sera of HCV-related CLD associated with autoimmune thyroiditis. On the other hand, antibodies to SS-A/Ro and/or SS-B/La, and rheumatoid factor (RF) are frequently observed in HCV-related CLD with Sjögren's syndrome (sicca syndrome), and rheumatoid arthritis, respectively.

In contrast, patients with HCV-related CLD seropositive for immunoglobulin G (IgG) type of antibodies to cardiolipin (CL) do not show the clinical features of anti-phospholipid antibody syndrome including thrombocytopenia and thrombosis. Moreover, the occurrence of autoantibodies to proliferating cell nuclear antigen (PCNA) is apparent in patients with HCV-related CLD who lack clinical symptoms of systemic lupus erythematosus (SLE). The occurrence of autoantibodies to platelets is also independent of thrombocytopenia.

Interestingly, autoantibodies to tumor-associated antigens including anti-p53, anti-survivin, and anti-Golgi proteins are found in sera of patients with HCV-related CLD.

Mechanisms for the production of autoantibodies in HCV-related CLD

Molecular mimicry between the HCV polyprotein and "self" proteins may account for the production of autoantibodies in chronic HCV infection. A sequence homology between the HCV polyprotein and cytochrome p450 2D6 (CYP 2D6), the antigenic target of anti-LKM1, was previously reported⁽¹³⁾. The reactivity against the viral protein would induce the production of anti-LKM1 in HCV-related CLD.

Gregorio and colleagues documented molecular mimicry between HCV polyprotein and three nuclear host antigens including matrin, histone H₂, and replication protein A as a mechanism for the emergence of ANA⁽¹⁴⁾. They also exhibited that the HCV polyprotein had sequence similarities to host smooth muscle antigens such as smoothelin, myosin, and vimentin. It is of interest that molecular mimicry between the HCV core protein and CENP-A, one of the three major target antigens of anticentromere antibodies, was elucidated⁽¹⁵⁾.

Polyclonal B cell activation by persistent HCV infection has been proposed as another mechanism for the production of autoantibodies. Polyclonal B cell activation seems to be essential for the development of certain autoimmune disorders including Sjögren's syndrome, and mixed cryoglobulinemia⁽¹⁶⁾. In determining one of the mechanisms for polyclonal B cell activation, Pileri and colleagues recently documented that HCV envelope protein (E2) represented a costimulatory signal to B cells by binding to CD 81 (tetraspanin) and thereby facilitated the production of autoantibodies⁽¹⁷⁾. A current study revealed that B-lymphocyte activating factor (BAFF) appeared to play a crucial role in HCV-induced autoimmunity⁽¹⁸⁾. Toibi and colleagues provided the evidence that the elevation of serum BAFF level is associated with the occurrence of antibodies to cardiolipin (CL)⁽¹⁹⁾.

Association of autoantibodies with clinicopathological parameters

In general, patients with chronic HCV infection with ANA had significantly higher age at entry and were female-dominant, compared with those without ANA⁽⁹⁾. The occurrence of ANA was independent of HCV genotypes or virus load^(9, 10, 20). Biochemical analysis revealed significantly higher serum levels of gamma-glutamyltranspeptidase (γ -GTP) and/or alkaline phosphatase (ALP) as well as

Table 1. Autoantibodies in HCV-related chronic liver disease.

Autoantibodies	Methodology	Target Antigen	Frequency	References
serological markers for autoimmune liver diseases				
ANA	IIF	matrin, histone H2A, replication protein A centromere	8%-54%	(9-12, 14, 69-71)
SMA	IIF	smoothelin, myosin, vimentin	10%-75%	(9, 11, 12, 14, 69, 71)
Anti-LKM1	IIF, WB, ELISA, IP	CYP 2D6, CYP 2A6	0%-13%	(9, 11, 69-71, 73, 75)
Anti-LC1	WB, IP	formiminotransferase cyclodeaminase	5%-12%	(29, 76)
anti-SLA	ELISA	UGA supressor tRNA-associated protein	0%-10%	(30, 31)
cANCA	IIF, ELISA	proteinase 3	56%-79%	(37, 65, 73)
pANCA	IIF, ELISA	myeloperoxidase	3%-4%	(65, 73, 75, 77)
AMA	IIF, WB, ELISA	PDH-E2	0%-8%	(11, 35, 57, 65, 69, 71, 73, 75)
anti-E3	WB, ELISA	dihydroliipoamide dehydrogenase	54%	(37)
PCA	IIF	H ⁺ ,K ⁺ -ATPase	7%-16%	(65, 73, 78)
anti-ASGPR	RIA	asialoglycprptein receptor	14%-15%	(32, 33)
serological markers for autoimmune diseases				
TMHA	passive hemagglutinin test	thyroid microsome	6%-29%	(55, 56, 69, 78-83)
TGHA	passive hemagglutinin test	thyroglobulin	1%-13%	(55, 69, 78-84)
TPO	RIA	thyroid peroxidase	2%-15%	(82, 84, 85)
RF	latex fixation test, nephelometry	Fc of IgG	15%-76%	(37, 71, 79, 86)
anti-SS-A/Ro	ELISA	Y1-Y5RNA binding proteins (52 kD, 60 kD)	1%-21%	(37, 44, 81, 87)
anti-SS-B/La	ELISA	48 kD RNA-binding protein	4%-23%	(37, 81, 88, 89)
anti-PCNA	WB, ELISA	DNA polymerase & auxiliary factor	17%-19%	(90, 91)
anti-CCP	ELISA	cyclic citrullinated peptide	0%-9%	(86, 92-94)
anti-CL	ELISA	cardiolipin	3%-44%	(37, 73, 95-97)
anti-C1q	ELISA	C1q	26%-38%	(34, 98)
anti-endothelial cell	ELISA	β2-GPI?, myeloperoxidase?	41%	(99)
anti-ribosomal P protein	ELISA	p0, p1, p2	3%	(100)
autoantibodies to endocrine organs				
anti-GAD	RIA	glutamic acid decarboxylase	3%-4%	(78, 101, 102)
anti-islet cells	IIF	sialic acid residue of glycolipid	0%-5%	(101-103)
anti-IA2	RIA	tyrosine phosphatase-like proteins	2%	(101, 102)
anti-insulin	RIA	insulin	2%	(103)
anti-adrenal cortex	IIF	21-hydroxylase	1%	(101)
autoantibodies to tumor-associated antigens				
anti-p53	WB, ELISA	p53 protein	0%-6%	(58, 104)
anti-IMPs	WB, ELISA	IGF-II mRNA-binding proteins	0%-5%	(59)
anti-survivin	WB, ELISA	survivin	18%	(105)
anti-Golgi	IIF, WB	Golgi protein	?	(106)
Others				
anti-platelet antibodies	MAIPA	GPIIb/IIIa	66%-81%	(107, 108)
anti-HLA antibodies	ELISA	HLA class I, class II	22%, 16%	(109)

Abbreviations are the same as in the text. IIF: indirect immunofluorescence; WB: western blot; ELISA: enzyme-linked immunosorbent assay; IP: immunoprecipitation; RIA: radioimmunoassay; MAIPA: monoclonal antibody-specific immobilization of platelet antigen assay; IA2: second islet cell autoantigens; β2-GPI: beta-2 glycoprotein; I, IGF-II: insulin-like growth factor II; GPIIb/IIIa: glycoprotein IIb/IIIa; HLA: human leukocyte antigens.

those of serum alanine aminotransferase (ALT) and IgG levels in patients with chronic hepatitis C (CH-C) with ANA than those without ANA (11, 12). Elevation of serum γ -GTP and ALP levels in patients with chronic hepatitis C seemed to be associated with bile duct lesions in the liver (21). Patients with HCV-related CLD seropositive for ANA commonly showed speckled pattern on HEP-2 cells (9, 12, 14). Histologically, CH-C patients with ANA had more severe hepatic fibrosis and inflammation than CH-C patients without ANA (9, 21). However, there was no significant difference in the incidence of lymphoid follicles between ANA-positive and ANA-negative patients with chronic hepatitis C (22).

Patients with CH-C seropositive for anti-LKM1 exhibited a predominance in males, had low titers of the antibodies (23), and mild activity in the liver (23-25), while patients with AIH type 2 were ordinarily young females with severe hepatic necroinflammation with high titers of anti-LKM1 (26). Patients with CH-C seropositive for anti-LKM1 seemed to be more susceptible to autoimmune thyroid disorders (24, 27). Interestingly, anti-LKM1 in chronic HCV infection is often associated with the emergence of ANA (24).

Patients with HCV-related CLD seropositive for anti-LC1 were also older and had less activity in the liver than patients with AIH type 2 who had anti-LC1 (28). The reactivity of antibodies to LC-1 in patients with chronic hepatitis C appears to be different from that in patients with AIH type 2 (29). Coincident emergence of anti-LKM1 was observed in one-third of patients with chronic hepatitis C with anti-LC1 (29).

Vitozzi and colleagues revealed that anti-SLA was detected in around 10% of Caucasian patients with HCV-related CLD (30), while Japanese patients with HCV-related CLD rarely had anti-SLA (25, 31). The isotype of the autoantibody was restricted to IgG₁ and IgG₄ (30). The coincident emergence of anti-SLA and anti-LKM1 seems to be controversial in patients with HCV-related CLD (29, 30).

The titers of antibodies to ASGPR in patients with AIH frequently reflected the disease severity (22). However, antibodies to ASGPR in patients with CH-C were independent of histological activities in the liver, and of the response to the treatment with IFN (32). The IgG subclass of anti-ASGPR in patients with CH-C was different from that in AIH: those with CH-C with anti-ASGPR showed IgG₄ predominance, while those with AIH showed IgG₂ predominance (33). Interestingly, the elevation of serum IgG levels was rarely observed in patients with chronic hepatitis C with CH-C seropositive for

anti-ASGPR (32).

Saadoun, *et al*, more recently documented that patients with CH-C seropositive for autoantibodies to C1q (anti-C1q) had significantly low levels of C4, compared with those without anti-C1q. There were no association between the prevalence of anti-C1q and HCV genotypes, or severity of histological findings in the liver (34).

Clinical features of patients with CH-C seropositive for antimitochondrial antibodies (AMA) were not different from those without AMA (35). AMA in sera of patients with CH-C were unlikely to recognize the same epitopes as those in primary biliary cirrhosis (PBC) (35). The results of a recent study revealed a high prevalence of antibodies to dihydrolipoamide dehydrogenase (E3) (36) in patients with HCV-related CLD (37).

Correlation of autoantibodies with HLA haplotypes

Genetic background for immunological features in HCV-related CLD has been analyzed. Czaja and colleagues demonstrated that Caucasian patients with chronic viral hepatitis including chronic hepatitis B and C were significantly associated with human leukocyte antigens (HLA) A1, B8, and DR3 haplotypes (38).

The patients with chronic viral hepatitis and concurrent autoimmune disorders commonly had HLA DR4 (38).

There are several interesting articles on the association of the HLA phenotypes with the emergence of anti-LKM1. Muratori and colleagues suggested the possibility of the genetic basis for the different geographic prevalence of anti-LKM1 in patients with CH-C (39). They revealed the close association between HLA DR7 and anti-LKM1 in Italian patients with CH-C. The low prevalence of HLA DR7 may contribute to the rarity of these autoantibodies in North America (39). On the other hand, the occurrence of anti-LKM1 in Japanese patients with HCV-related CLD was not restricted to HLA DR4 (40), which proved to be a genetic predisposing factor for AIH type 1 in Japan (41). Interestingly, Bogdanos, *et al*, disclosed that patients with HCV-related CLD seropositive for anti-LKM1 who possessed HLA B51 showed cross-reactivity of HCV E1 protein and the amino acid sequence 257-271 of CYP2D6-the major B cell auto-epitope of CYP2D6 (42).

Sicca syndrome in chronic HCV infection depended on HLA DQB1*02 haplotype (43). None of the patients who restricted to the haplotype of

HLA DQB1*02 had antibodies to SS-A/Ro, or SS-B/La (43). Interestingly, the prevalence of HLA DR2 in patients with HCV-related CLD seropositive for anti-SS-B/La was significantly lower than that in HCV-related CLD seronegative for anti-SS-B/La (44).

It has been well known that treatment with IFN frequently induces the production of autoantibodies in patients with CH-C. Kamizaki and colleagues previously revealed that HLA A2 was highly linked to IFN-induced autoimmune thyroiditis in patients with CH-C (45). The association of HLA DRB1*11 haplotype with IFN-induced autoimmune thyroiditis was also reported in a Caucasian population (46).

On the other hand, autoantibodies to GAD and/or islet cells were induced in patients with chronic hepatitis C who possessed the diabetic associated HLA DR3 (DRB *03011, DQA1 *0501, DQB1 *0201) during the treatment with IFN; these patients, thereafter developed type 1 diabetes mellitus (DM) (47).

Possible indicators for concurrent diseases or prognosis

The emergence of several types of autoantibodies in patients with chronic HCV infection suggests concurrent autoimmune disorders. IgG antibodies to cardiolipin (CL) are frequently detected in patients with HCV-related CLD regardless of anti- β_2 -glycoprotein I (48). Cojocar, *et al*, recently found that high titers of IgG anti-CL were strongly associated with acute ischemic stroke (49). There are several interesting studies the results of which indicate that IgG anti-CL may predict the occurrence of lichen planus (50) or mixed cryoglobulinemia (51) in patients with HCV-related CLD.

Rheumatoid factor (RF) appeared to be more common in HCV-related sicca syndrome than in HCV-negative sicca syndrome (52, 53). However, antibodies to SS-A/Ro or SS-B/La appeared to be rare in patients with HCV-positive sicca syndrome (53). Ramos-Casals and colleagues investigated the characteristics of B cell lymphoma in patients with Sjögren's syndrome and HCV-related CLD (54), suggesting the close association between RF and B cell lymphoma complicating Sjögren's syndrome and HCV infection.

Thyroid autoantibodies are commonly observed in patients with HCV-related CLD. TMHA are frequently useful to detect latent autoimmune thyroiditis in patients with CH-C prior to antiviral

treatment (55). It is of interest that TMHA may predict thyroid dysfunction including hyperthyroidism and hypothyroidism (56).

Patients with CH-C seropositive for anti-E3 frequently progressed to liver cirrhosis and arthritis (37). Another group of investigators revealed that AMA in chronic HCV infection was mostly associated with systemic autoimmune diseases including Sjögren's syndrome, systemic sclerosis, and SLE (57). The relationship between the emergence of ANCA and skin diseases such as rash, purpura, nodules, livedo reticularis and Raynaud's phenomenon is also known (37).

We recently documented that autoantibodies to tumor-associated antigens including p53 and insulin-like growth factor II mRNA-binding proteins (IMPs) are present in sera of patients with hepatocellular carcinoma (HCC) (58, 59). Retrospective analysis showed that anti-p53, and anti-IMP1 in a patient with HCV-related CLD were detected prior to occurrence of HCC. This finding indicate that these autoantibodies may predict the progression of HCC in patients with HCV-related CLD.

In addition, Mozo and colleagues noted that anti-Golgi antibodies may emerge in HCV-induced malignant transformation (60). Anti-Golgi antibodies were found in two (6%) of 36 patients with virus-induced HCC. They speculated that both viral infection and malignant transformation might trigger the production of anti-Golgi antibodies (60).

Treatments for patients with chronic hepatitis C seropositive for autoantibodies

Overall, the presence of autoantibodies such as ANA or anti-LKM1 in patients with CH-C is less likely to affect the response to antiviral treatment (9, 61-64). Therefore, IFN is often administrated to patients with CH-C seropositive for such kinds of autoantibodies. Gatselis, *et al*, demonstrated that the positivity for ANA at the end of the treatment and the increase of SMA titers during the treatment might be possible indicators for a poor response to IFN therapy (65).

The type of treatment (combination therapy of IFN or pegylated IFN with ribavirin vs IFN or pegylated IFN alone) was generally independent of the occurrence of autoantibodies at the end of treatment or follow-up (65). It is worthy to note that the additional administration of ribavirin to IFN in patients with CH-C does not affect thyroid autoantibody status but increases the risk of hypothyroidism. (66).

The emergence of autoantibodies or elevation of the titers by administration of IFN was strictly associated with the genetic factors in hosts, as described above. The antiviral treatment occasionally induces the autoimmunity in patients with CH-C. Such patients eventually require treatment with corticosteroid (67, 68).

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