



WJG 20th Anniversary Special Issues (11): Cirrhosis

Autoantibodies in primary biliary cirrhosis: Recent progress in research on the pathogenetic and clinical significance

Satoshi Yamagiwa, Hiroteru Kamimura, Masaaki Takamura, Yutaka Aoyagi

Satoshi Yamagiwa, Hiroteru Kamimura, Masaaki Takamura, Yutaka Aoyagi, Division of Gastroenterology and Hepatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata 951-8510, Japan

Author contributions: All authors contributed to the analysis of pertinent literature and to the writing of the manuscript.

Correspondence to: Satoshi Yamagiwa, MD, PhD, Division of Gastroenterology and Hepatology, Niigata University Graduate School of Medical and Dental Sciences, 757 Asahimachi-dori 1, Chuo-ku, Niigata 951-8510,

Japan. syamagi@med.niigata-u.ac.jp

Telephone: +81-25-2272207 Fax: +81-25-2270776

Received: October 26, 2013 Revised: November 22, 2013

Accepted: January 8, 2014

Published online: March 14, 2014

Abstract

Primary biliary cirrhosis (PBC) is a chronic progressive cholestatic liver disease characterized by immune-mediated destruction of the small- and medium-sized intrahepatic bile ducts and the presence of anti-mitochondrial antibodies (AMA) in the serum. AMA are detected in over 90% of patients with PBC, whereas their prevalence in the general population is extremely low, varying from 0.16% to 1%. Previous studies have shown that the unique characteristics of biliary epithelial cells undergoing apoptosis may result in a highly direct and very specific immune response to mitochondrial autoantigens. Moreover, recent studies have demonstrated that serum from AMA-positive PBC patients is reactive with a number of xenobiotic modified E2 subunits of the pyruvate dehydrogenase complex, which is not observed in the serum of normal individuals. These findings indicate that chemicals originating from the environment may be associated with a breakdown in the tolerance to mitochondrial autoantigens. While it is currently generally accepted that AMA are the most specific serological markers of PBC, more than 60 au-

toantibodies have been investigated in patients with PBC, and some have previously been considered specific to other autoimmune diseases. This review covers the recent progress in research on the pathogenetic and clinical significance of important autoantibodies in PBC. Determining the pathogenic role of those autoantibodies in PBC remains a priority of basic and clinical research.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Primary biliary cirrhosis; Autoantibodies; Anti-mitochondrial antibodies; Anticentromere antibodies; Anti-gp210 antibodies

Core tip: While the presence of antimitochondrial antibodies is pathognomonic to Primary biliary cirrhosis (PBC), more than 60 autoantibodies have been detected in patients with PBC. Antinuclear antibodies (ANA) become positive in approximately 30% to 50% of patients with PBC. Among ANA, anti-gp210 and anticentromere antibodies have been indicated as significant prognostic markers. Previous studies have shown that unique characteristics of biliary epithelial cells during apoptosis may result in the presence of a direct and specific immune response to mitochondrial autoantigens. Moreover, recent studies have indicated that chemicals originating from the environment are associated with a breakdown in the tolerance against mitochondrial autoantigens.

Yamagiwa S, Kamimura H, Takamura M, Aoyagi Y. Autoantibodies in primary biliary cirrhosis: Recent progress in research on the pathogenetic and clinical significance. *World J Gastroenterol* 2014; 20(10): 2606-2612 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i10/2606.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i10.2606>

INTRODUCTION

Primary biliary cirrhosis (PBC) is a chronic progressive cholestatic liver disease characterized by immune-mediated destruction of small- and medium-sized intrahepatic bile ducts and the presence of antimitochondrial antibodies (AMA) in serum of affected patients^[1,2]. PBC is considered a model autoimmune disease on the basis of several features, including the presence of a highly direct and very specific immune response to mitochondrial autoantigens, female predominance, and homogeneity among patients^[3]. Despite the fact that the mitochondrial targets are ubiquitous proteins expressed in all nucleated cells, the immunopathology of PBC is characterized by the presence of CD4⁺ and CD8⁺ T-cell infiltrates in the liver and targeted destruction of biliary epithelial cells (BECs)^[4,5]. This suggests that BECs may have unique immunological characteristics. While it is currently accepted that AMA are the most specific serological markers of PBC, more than 60 autoantibodies have been investigated in PBC patients, some having previously been considered specific for other autoimmune diseases^[6].

The immune system has an extraordinary capacity of preventing self-antigens from provoking an inflammatory reaction. Therefore, the presence of autoantibodies is the consequence of a breakdown in or complete failure of B cell tolerance to corresponding autoantigens^[7]. However, antibodies against self-antigens are also found in cancer, during massive tissue damage, and even in healthy subjects. Natural autoantibodies (NAAs) are immunoglobulins produced at tightly regulated levels in the complete absence of external antigenic stimulation^[7]. Although NAAs have long been considered a sign of a breakdown in tolerance, these antibodies appear to play an important role in the innate immune system as a first line of defense against pathogens as well as in the prevention of autoimmune diseases^[8,9]. It was recently demonstrated that NAAs bind to apoptotic cells and thereby facilitate their uptake by dendritic cells, thus preventing activation of the adaptive immune system by molecules released upon apoptosis, which may trigger autoimmune events^[7,10]. Considering the many nonspecific autoantibodies are detected in patients with PBC, we speculate that these antibodies may be NAAs that are not associated with the development of autoimmunity. Interestingly, the majority of NAAs are of the IgM type, with a smaller proportion of IgG and IgA types^[11]. The elevated serum IgM level, which is a well-known characteristic of PBC, may reflect such an increase of IgM-type NAAs, although recent studies have stressed that environmental factors also play a major role^[12,13]. However, the importance of innate immunity, including NAAs, in autoimmune responses has been only recently appreciated, and its role remains to be clarified. The present review focuses mainly on recent progress in studies of the pathogenetic and clinical significance of the more significant autoantibodies detected in PBC patients.

ANTIMITOCHONDRIAL ANTIBODIES

AMA are detected in over 90% of patients with PBC, whereas their prevalence in the general population is extremely low, varying between 0.16% and 1%, and only reaching 8% in hepatitis C virus (HCV)-infected patients^[13]. AMA seropositivity is a strong predictor for the development of PBC. Mitchison *et al.*^[14] found that only two of 29 AMA-positive healthy patients had a normal liver histology pattern. Ten years later, 76% of those patients had developed clinical signs and symptoms of PBC^[14,15]. Thus, despite their high predictive value, AMA are not useful for prognostication in terms of clinical course of PBC. Moreover, most studies indicate that AMA levels are unaffected by treatment^[13].

The autoantigens of AMA have been identified as the E2 subunits of the 2-oxo-acid dehydrogenase complexes, including the E2 subunits of the pyruvate dehydrogenase complex (PDC-E2), branched chain 2-oxo acid dehydrogenase complex, 2-oxo-glutarate dehydrogenase complex, and the E3 binding protein of dihydrolipoamide dehydrogenase^[5,16-18]. The AMA target antigens are all localized within the inner mitochondrial matrix and catalyze the oxidative decarboxylation of 2-oxo-acid acid substrates^[5,19]. In approximately 95% of patients, AMA are directed towards the 74 kD mitochondrial polypeptide identified as PDC-E2. During apoptosis of BECs, PDC-E2 remains immunologically intact without being glutathiolated, and becomes the source of the PDC-E2 apotope. The term apotope specifies an epitope created during the processes of apoptosis^[20,21]. PDC-E2 contained within apoptotic bodies can be recognized by circulating AMA, and the resulting apotope-AMA complex then stimulates the innate immune systems in genetically susceptible individuals^[21]. Immune destruction is restricted to BECs due to their unique physiology and is exacerbated by retention of PDC-E2 in apoptotic blebs resulting from apoptosis of BECs^[21]. Several previous studies of the liver in PBC patients have reported accentuated apical expression of PDC-E2 in BECs, and induction of PDC-E2 cell-surface expression during BEC autophagy^[22]. The accumulation of autophagic vacuoles appears to be critical for the cell-surface expression of PDC-E2, and such expression may play a role in antigen presentation on BECs, followed by autoimmune-mediated cell injuries of BECs^[22].

Association between xenobiotic and antimitochondrial antibodies

Although bacteria and viruses may induce PBC through molecular mimicry, other environmental factors, xenobiotics, or chemical compounds foreign to a living organism may exert similar effects^[18]. Previous analysis of the specificity of anti-PDC-E2 has revealed a number of anti-PDC-E2 antibody subpopulations that recognize either the PDC peptide, PDC peptide conjugated with lipoic acid, or lipoic acid itself^[23,24]. The immunodominant

epitope of PDC-E2 is the lipoylated domain, and the lipoy acid residue attached to AMA epitopes is necessary for autoantibody binding^[24]. Moreover, recent studies involving quantitative structure-activity relationship analysis have demonstrated that serum from AMA-positive PBC patients, but not that from controls, is reactive with a number of xenobiotic modified PDC-E2 structures^[25]. These findings indicate that chemicals of environmental origin may be associated with the breakdown of tolerance to mitochondrial autoantigens.

ANTINUCLEAR ANTIBODIES

Antinuclear antibodies (ANA) are serological markers that can be found in a wide variety of liver diseases (drug-induced, viral, alcoholic hepatitis, nonalcoholic steatohepatitis, AIH, PBC, and PSC) and non-hepatic autoimmune diseases (Hashimoto thyroiditis, systemic lupus erythematosus, Sjögren syndrome), as well as in a subgroup of healthy individuals, though usually at a low titer levels^[12]. Antinuclear indirect immunofluorescence patterns are characterized by anti-multiple nuclear dots, rim-like/membrane antibodies and less specific anticentromere antibodies (ACA). The molecular target of anti-multiple nuclear dots is the protein sp100 and the promyelocytic leukemia (PML) protein^[12,26]. The anti-rim-like/membranous antibodies are mainly represented by the protein glycoprotein (gp)-210^[12,27]. Muratori *et al.*^[28] demonstrated that ANA were present in almost 50% of patients with PBC and that their prevalence reached 85% in AMA-negative sera. Specifically, 27% of patients had anti-sp100, 16% had anti-gp210, and 16% had anticentromere antibodies. In other reports, the prevalence of ANA in PBC patients has been approximately 30%-50%^[12]. Although the significance and predictive value of ANA have been confirmed in other autoimmune diseases such as type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease, the predictive significance of ANA in PBC remains unclear^[20,29].

Anticentromere antibodies

In patients with calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome or limited cutaneous systemic sclerosis, ACA positivity may be as high as 50%-90%. Although they are not specific to systemic sclerosis, ACA are usually associated with a good prognosis for that condition^[6,30]. In patients with PBC, the ACA positivity rate is approximately 30%^[6]. Nakamura *et al.*^[31] conducted a retrospective multi-center cohort study of 276 patients with biopsy-confirmed PBC, and found that positivity for ACA was a significant risk factor for the development of portal hypertension. The findings from histological observations indicate that the presence of ACA is most significantly associated with a relatively severe ductular reaction^[31]. In PBC, the production of cytokines or growth factors from

inflammatory cells, rather than retention of bile constituents, is potentially critical for the induction of ductular reaction^[32]. In chronic hepatitis, this type of ductular reaction is also known to promote fibrosis *via* the production of transforming growth factor- β , monocyte chemoattractant protein-1, and platelet-derived growth factor by proliferating ductular epithelia^[33,34]. Therefore, it is reasonable to speculate that more severe ductular reaction may play a crucial role in the progression to portal hypertension in PBC patients who are ACA-positive. However, the mechanism of bile duct damage appears to lead to chronic cholestasis and development of biliary cirrhosis, even in ACA-positive patients^[20,35].

Antinuclear pore antibodies (gp210)

A number of nuclear antigens have been recognized as targets of ANA in patients with PBC, including several components of the nuclear pore complex, such as the gp210 and p62 proteins^[6]. Gp210 is an integral glycoprotein of the nuclear pore consisting of three main domains: a large glycosylated luminal domain, a single hydrophobic transmembrane segment, and a short cytoplasmic tail. Gp210 is recognized by antibodies in approximately 25% of patient with PBC^[6,36]. The association between the presence of anti-gp210 antibodies and the outcome of PBC was first reported by Itoh *et al.*^[37], and subsequently confirmed by several additional studies^[38-40]. Ishibashi *et al.*^[20] and Nakamura *et al.*^[41] reported that PBC patients with consistently high levels of anti-gp210-C terminal peptide antibody have a higher risk of progression to end-stage hepatic failure than do those without such antibodies, or those in whom antibody levels are initially positive but drop to low levels after treatment with ursodeoxycholic acid. These reports demonstrate that antibodies against nuclear pore complexes, especially gp210-C terminal peptides, may serve as important surrogate predictors of PBC progression to end-stage hepatic failure. It has been shown that the presence of anti-gp210 antibodies was most significantly associated with more severe interface hepatitis and lobular inflammation^[31]. Furthermore, there was a tendency for relatively more severe ductopenia (ductular reaction) in late stages of disease anti-gp210-positive patients^[31]. These findings suggest that two main processes - bile duct destruction and interface hepatitis - are more severe in PBC patients positive for anti-gp210 antibodies compared to those negative for anti-gp210 antibodies; thus, leading to more frequent progression to end-stage hepatic failure^[20,31]. Nakamura *et al.*^[42] found that expression of gp210 antigens was increased on the nuclear envelope of epithelial cells in small bile ducts in the liver of PBC patients and that the intensity of gp210 staining by immunofluorescence was positively correlated with the intensity of inflammation around small bile ducts. These observations indicate that gp210 may be a target antigen, reactivity against which plays an important role in both bile duct destruction and interface hepatitis.

Table 1 Serum autoantibodies in primary biliary cirrhosis

Autoantibody	Prevalence	Comments	Ref.
Related to the diagnosis and prognosis of PBC			
AMA	90%-95%	Diagnostic value	[1]
Anti-sp100	30%-50%	Diagnostic value	[13,43-46]
Anti-gp210	30%-50%	Possible prognostic value (hepatic failure)	[6,31,36-42]
Anticentromere antibodies	16%-30%	Possible prognostic value (portal hypertension)	[6,30-35]
Anti-p97/VCP	12.5%	Possible prognostic value (favorable)	[48-50]
Anti-EPO	52.5%	Diagnostic value Less peripheral eosinophils	[51]
Anti-β2GPI	2%-15%	Possible prognostic Value (poor)	[52,53]
Related to the pathogenesis of PBC			
ASCA	24.2%	Enhanced mucosal immunity	[54-56]
Anti-ClpP	30%-47%	Infectious factor	[57,58]
Anti-β-subunit of bacterial RNA polymerase	32.8%	Bacterial triggers	[59]
Related to other autoimmune diseases			
Anti-SMA	8.0%-25.0%	PBC-AIH overlap	[6,40,60]
Anti-dsDNA	17.0%-22.0%	PBC-AIH overlap	[39,61,62]
Anti-SSA	5.0%-33.0%	Sjogren syndrome	[63,64]
Anti-CCP	2.7%-4.0%	Rheumatoid Arthritis	[65-67]

PBC: Primary biliary cirrhosis; CCP: Cyclic cirtullinated peptide; SMA: Smooth muscle antigen; ClpP: Caseinolytic protease P; ASCA: Antisaccharomyces cerevisiae antibodies; EPO: Eosinophil peroxidase; β2GPI: β(2)-glycoprotein I; VCP: Valosin containing protein; AMA: Antimitochondrial antibodies.

Antinuclear dot antibodies (Anti-sp100)

Sp100 was discovered in the context of leukemic transformation and as an autoantigen in PBC^[43]. Sp100 antigen is a 480 amino acid peptide with a calculated molecular weight of 53 kDa that shows aberrant electrophoretic mobility to 100 kDa^[44]. The prevalence of anti-sp100 antibodies in patients with PBC is approximately 25%. Anti-sp100 antibody, which has a specificity of 94%, has an important diagnostic role in PBC, particularly in AMA-negative patients^[26,45,46]. However, anti-sp100 antibodies have been increasingly found in many other autoimmune diseases, including systemic lupus erythematosus and systemic sclerosis. Interestingly, among PBC patients, approximately 74% of those with urinary tract infections are positive for anti-sp100, whereas the positivity rate is only 4.8% in those without such infections^[6,47]. Given the high specificity of anti-sp100 as an immunoserological hallmark of PBC, these findings support the hypothesis that some bacterial infections might be involved in the induction of PBC-specific autoimmunity.

OTHER AUTOANTIBODIES IN PBC

Other autoantibodies against nuclear constituents (dsDNA, ssDNA, histone, scl-70, Sm, SSA-SSB, RNP, Jo-1, U1RNP) have also been detected in PBC, mostly in con-

junction with rheumatic co-morbidities^[6]. Anti-p97/VCP (valosin containing protein) antibodies are detected in approximately 12.7% of PBC cases, and their presence suggests a less progressive disease course and a benign prognosis^[48-50]. Eosinophil peroxidase (Anti-EPO) antibodies have been detected in 52.5% of patients with PBC and 29.0% of patients with AIH. PBC patients who were positive for anti-EPO antibodies had a significantly smaller number of peripheral eosinophils than did patients who were anti-EPO negative^[51]. As mentioned above, more than 60 autoantibodies have been detected in PBC patients, but some are not specific for any disease, while some are thought to be more closely related to other autoimmune diseases^[6]. Among those autoantibodies, the more significant autoantibodies detected in PBC patients are summarized in Table 1^[6,13,48-68]. A comprehensive review of these autoantibodies in PBC was published by Hu *et al*^[6] in 2010.

Line immune assay

Previous studies of autoantibodies in PBC have primarily focused on only a single type of autoantibody, whereas the positivity pattern of different autoantibodies in a single serum sample, as well as their clinical significance, have not been elucidated. A line immune assay (LIA) kit that can simultaneously measure different autoantibodies known to be involved in autoimmune disease has recently become available and has been employed in clinical practice. Using a LIA kit that can detect 9 autoantibodies against AMA-M2, M2-3E (a fusion protein of the E2 subunits of alpha-2-oxoacid dehydrogenases of the inner mitochondrial membrane), sp100, PML, gp210, Ro-52, LKM-1 (liver-kidney microsomes-1), LC-1 (cytosolic liver antigen type 1), and SLA/LP (soluble liver antigen/liver-pancreas antigen), Saito *et al*^[68] examined the prevalence and positivity pattern of those autoantibodies in 80 patients with PBC, 40 patients with AIH, and 16 patients with PBC-AIH overlap. They found that the prevalence of positivity for anti-sp100, anti-PML, anti-gp210, anti-Ro-52, and ACA were 13.8%, 8.7%, 40%, 27.5%, and 32.5% in PBC, respectively. In the PBC-AIH overlap group, the prevalence of both anti-gp210 (68.7%) and anti-Ro-52 (81.2%) were significantly higher than those in the PBC and AIH groups. The authors concluded that LIA is useful for the diagnosis of PBC and PBC-AIH overlap, although AMA-M2 should be measured by the conventional ELISA-based method, as LIA is less sensitive than ELISA in detecting AMA^[68].

CONCLUSION

We have provided an overview of the recent developments in the general understanding of the pathogenetic and clinical significance of the autoantibodies that significantly impact PBC. Although there have been substantial advances, determining the pathogenic role of autoantibodies in PBC remains a priority of basic and clinical research.

REFERENCES

- 1 **Kaplan MM**, Gershwin ME. Primary biliary cirrhosis. *N Engl J Med* 2005; **353**: 1261-1273 [PMID: 16177252 DOI: 10.1056/NEJMra043898]
- 2 **Selmi C**, Bowlus CL, Gershwin ME, Coppel RL. Primary biliary cirrhosis. *Lancet* 2011; **377**: 1600-1609 [PMID: 21529926 DOI: 10.1016/S0140-6736(10)61965-4]
- 3 **Uibo R**, Kisand K, Yang CY, Gershwin ME. Primary biliary cirrhosis: a multi-faced interactive disease involving genetics, environment and the immune response. *APMIS* 2012; **120**: 857-871 [PMID: 23009110 DOI: 10.1111/j.1600-0463.2012.02914.x]
- 4 **Gershwin ME**, Mackay IR. The causes of primary biliary cirrhosis: Convenient and inconvenient truths. *Hepatology* 2008; **47**: 737-745 [PMID: 18098322 DOI: 10.1002/hep.22042]
- 5 **Leung PS**, Wang J, Naiyanetr P, Kenny TP, Lam KS, Kurth MJ, Gershwin ME. Environment and primary biliary cirrhosis: electrophilic drugs and the induction of AMA. *J Autoimmun* 2013; **41**: 79-86 [PMID: 23352659 DOI: 10.1016/j.jaut.2012.12.007]
- 6 **Hu CJ**, Zhang FC, Li YZ, Zhang X. Primary biliary cirrhosis: what do autoantibodies tell us? *World J Gastroenterol* 2010; **16**: 3616-3629 [PMID: 20677333 DOI: 10.3748/wjg.v16.i29.3616]
- 7 **Lleo A**, Invernizzi P, Gao B, Podda M, Gershwin ME. Definition of human autoimmunity—autoantibodies versus autoimmune disease. *Autoimmun Rev* 2010; **9**: A259-A266 [PMID: 19963079 DOI: 10.1016/j.autrev.2009.12.002]
- 8 **Sauerborn M**, Schellekens H. B-1 cells and naturally occurring antibodies: influencing the immunogenicity of recombinant human therapeutic proteins? *Curr Opin Biotechnol* 2009; **20**: 715-721 [PMID: 19892544 DOI: 10.1016/j.copbio.2009.10.007]
- 9 **Kubo T**, Uchida Y, Watanabe Y, Abe M, Nakamura A, Ono M, Akira S, Takai T. Augmented TLR9-induced Btk activation in PIR-B-deficient B-1 cells provokes excessive autoantibody production and autoimmunity. *J Exp Med* 2009; **206**: 1971-1982 [PMID: 19687229 DOI: 10.1084/jem.20082392]
- 10 **Rosen A**, Casciola-Rosen L. Autoantigens in systemic autoimmunity: critical partner in pathogenesis. *J Intern Med* 2009; **265**: 625-631 [PMID: 19493056 DOI: 10.1111/j.1365-2796.2009.02102.x]
- 11 **Schwartz-Albiez R**, Monteiro RC, Rodriguez M, Binder CJ, Schoenfeld Y. Natural antibodies, intravenous immunoglobulin and their role in autoimmunity, cancer and inflammation. *Clin Exp Immunol* 2009; **158** Suppl 1: 43-50 [PMID: 19883423 DOI: 10.1111/j.1365-2249.2009.04026.x]
- 12 **Lleo A**, Liao J, Invernizzi P, Zhao M, Bernuzzi F, Ma L, Lanzi G, Ansari AA, Coppel RL, Zhang P, Li Y, Zhou Z, Lu Q, Gershwin ME. Immunoglobulin M levels inversely correlate with CD40 ligand promoter methylation in patients with primary biliary cirrhosis. *Hepatology* 2012; **55**: 153-160 [PMID: 21898485 DOI: 10.1002/hep.24630]
- 13 **Achenza MI**, Meda F, Brunetta E, Selmi C. Serum autoantibodies for the diagnosis and management of autoimmune liver diseases. *Expert Rev Gastroenterol Hepatol* 2012; **6**: 717-729 [PMID: 23237257 DOI: 10.1586/egh.12.58]
- 14 **Mitchison HC**, Bassendine MF, Hendrick A, Bennett MK, Bird G, Watson AJ, James OF. Positive antimitochondrial antibody but normal alkaline phosphatase: is this primary biliary cirrhosis? *Hepatology* 1986; **6**: 1279-1284 [PMID: 3793004 DOI: 10.1002/hep.1840060609]
- 15 **Metcalfe JV**, Mitchison HC, Palmer JM, Jones DE, Bassendine MF, James OF. Natural history of early primary biliary cirrhosis. *Lancet* 1996; **348**: 1399-1402 [PMID: 8937278 DOI: 10.1016/S0140-6736(96)04410-8]
- 16 **Gershwin ME**, Mackay IR, Sturgess A, Coppel RL. Identification and specificity of a cDNA encoding the 70 kd mitochondrial antigen recognized in primary biliary cirrhosis. *J Immunol* 1987; **138**: 3525-3531 [PMID: 3571977]
- 17 **Van de Water J**, Gershwin ME, Leung P, Ansari A, Coppel RL. The autoepitope of the 74-kD mitochondrial autoantigen of primary biliary cirrhosis corresponds to the functional site of dihydrolipoamide acetyltransferase. *J Exp Med* 1988; **167**: 1791-1799 [PMID: 2455013 DOI: 10.1084/jem.167.6.1791]
- 18 **Leung PS**, Chuang DT, Wynn RM, Cha S, Danner DJ, Ansari A, Coppel RL, Gershwin ME. Autoantibodies to BCO-ADC-E2 in patients with primary biliary cirrhosis recognize a conformational epitope. *Hepatology* 1995; **22**: 505-513 [PMID: 7543435 DOI: 10.1016/0270-9139(95)90572-3]
- 19 **Mao TK**, Davis PA, Odin JA, Coppel RL, Gershwin ME. Sidechain biology and the immunogenicity of PDC-E2, the major autoantigen of primary biliary cirrhosis. *Hepatology* 2004; **40**: 1241-1248 [PMID: 15558739 DOI: 10.1002/hep.20491]
- 20 **Ishibashi H**, Komori A, Shimoda S, Ambrosini YM, Gershwin ME, Nakamura M. Risk factors and prediction of long-term outcome in primary biliary cirrhosis. *Intern Med* 2011; **50**: 1-10 [PMID: 21212566 DOI: 10.2169/internalmedicine.50.4462]
- 21 **Lleo A**, Selmi C, Invernizzi P, Podda M, Coppel RL, Mackay IR, Gores GJ, Ansari AA, Van de Water J, Gershwin ME. Apoptoses and the biliary specificity of primary biliary cirrhosis. *Hepatology* 2009; **49**: 871-879 [PMID: 19185000 DOI: 10.1002/hep.22736]
- 22 **Sasaki M**, Miyakoshi M, Sato Y, Nakanuma Y. Increased expression of mitochondrial proteins associated with autophagy in biliary epithelial lesions in primary biliary cirrhosis. *Liver Int* 2013; **33**: 312-320 [PMID: 23231002 DOI: 10.1111/liv.12049]
- 23 **Bruggraber SF**, Leung PS, Amano K, Quan C, Kurth MJ, Nantz MH, Benson GD, Van de Water J, Luketic V, Roche TE, Ansari AA, Coppel RL, Gershwin ME. Autoreactivity to lipoate and a conjugated form of lipoate in primary biliary cirrhosis. *Gastroenterology* 2003; **125**: 1705-1713 [PMID: 14724823 DOI: 10.1053/j.gastro.2003.09.034]
- 24 **Selmi C**. The worldwide gradient of autoimmune conditions. *Autoimmun Rev* 2010; **9**: A247-A250 [PMID: 20144744 DOI: 10.1016/j.autrev.2010.02.004]
- 25 **Chen RC**, Naiyanetr P, Shu SA, Wang J, Yang GX, Kenny TP, Guggenheim KC, Butler JD, Bowlus C, Tao MH, Kurth MJ, Ansari AA, Kaplan M, Coppel RL, Lleo A, Gershwin ME, Leung PS. Antimitochondrial antibody heterogeneity and the xenobiotic etiology of primary biliary cirrhosis. *Hepatology* 2013; **57**: 1498-1508 [PMID: 23184636 DOI: 10.1002/hep.26157]
- 26 **Szosteck C**, Will H, Netter HJ, Guldner HH. Autoantibodies to the nuclear Sp100 protein in primary biliary cirrhosis and associated diseases: epitope specificity and immunoglobulin class distribution. *Scand J Immunol* 1992; **36**: 555-564 [PMID: 1384113 DOI: 10.1111/j.1365-3083.1992.tb03224.x]
- 27 **Courvalin JC**, Lassoued K, Bartnik E, Blobel G, Wozniak RW. The 210-kD nuclear envelope polypeptide recognized by human autoantibodies in primary biliary cirrhosis is the major glycoprotein of the nuclear pore. *J Clin Invest* 1990; **86**: 279-285 [PMID: 2195063 DOI: 10.1172/JCI114696]
- 28 **Muratori L**, Parola M, Ripalti A, Robino G, Muratori P, Bellomo G, Carini R, Lenzi M, Landini MP, Albano E, Bianchi FB. Liver/kidney microsomal antibody type 1 targets CY-P2D6 on hepatocyte plasma membrane. *Gut* 2000; **46**: 553-561 [PMID: 10716687 DOI: 10.1136/gut.46.4.553]
- 29 **Tzioufas AG**, Routsias JG. Idiotype, anti-idiotype network of autoantibodies: pathogenetic considerations and clinical application. *Autoimmun Rev* 2010; **9**: 631-633 [PMID: 20478412 DOI: 10.1016/j.autrev.2010.05.013]
- 30 **Vlachoyiannopoulos PG**, Drosos AA, Wiik A, Moutsopoulos HM. Patients with anticitromere antibodies, clinical features, diagnoses and evolution. *Br J Rheumatol* 1993; **32**: 297-301 [PMID: 8461923 DOI: 10.1093/rheumatology/32.4.297]

- 31 **Nakamura M**, Kondo H, Mori T, Komori A, Matsuyama M, Ito M, Takii Y, Koyabu M, Yokoyama T, Migita K, Daikoku M, Abiru S, Yatsuhashi H, Takezaki E, Masaki N, Sugi K, Honda K, Adachi H, Nishi H, Watanabe Y, Nakamura Y, Shimada M, Komatsu T, Saito A, Saoshiro T, Harada H, Sodeyama T, Hayashi S, Masumoto A, Sando T, Yamamoto T, Sakai H, Kobayashi M, Muro T, Koga M, Shums Z, Norman GL, Ishibashi H. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. *Hepatology* 2007; **45**: 118-127 [PMID: 17187436 DOI: 10.1002/hep.21472]
- 32 **Clouston AD**, Powell EE, Walsh MJ, Richardson MM, Demetris AJ, Jonsson JR. Fibrosis correlates with a ductular reaction in hepatitis C: roles of impaired replication, progenitor cells and steatosis. *Hepatology* 2005; **41**: 809-818 [PMID: 15793848 DOI: 10.1002/hep.20650]
- 33 **Lazaridis KN**, Strazzabosco M, Larusso NF. The cholangiopathies: disorders of biliary epithelia. *Gastroenterology* 2004; **127**: 1565-1577 [PMID: 15521023 DOI: 10.1053/j.gastro.2004.08.006]
- 34 **Gressner AM**, Weiskirchen R. Modern pathogenetic concepts of liver fibrosis suggest stellate cells and TGF-beta as major players and therapeutic targets. *J Cell Mol Med* 2006; **10**: 76-99 [PMID: 16563223 DOI: 10.1111/j.1582-4934.2006.tb00292.x]
- 35 **Nakamura M**, Komori A, Ito M, Kondo H, Aiba Y, Migita K, Nagaoka S, Ohata K, Yano K, Abiru S, Daikoku M, Yatsuhashi H, Shimoda S, Ishibashi H. Predictive role of anti-gp210 and anticentromere antibodies in long-term outcome of primary biliary cirrhosis. *Hepatol Res* 2007; **37** Suppl 3: S412-S419 [PMID: 17931196 DOI: 10.1111/j.1872-034X.2007.00244.x]
- 36 **Worman HJ**. Nuclear envelope protein autoantigens in primary biliary cirrhosis. *Hepatol Res* 2007; **37** Suppl 3: S406-S411 [PMID: 17931195 DOI: 10.1111/j.1872-034X.2007.00227.x]
- 37 **Itoh S**, Ichida T, Yoshida T, Hayakawa A, Uchida M, Tashiro-Itoh T, Matsuda Y, Ishihara K, Asakura H. Autoantibodies against a 210 kDa glycoprotein of the nuclear pore complex as a prognostic marker in patients with primary biliary cirrhosis. *J Gastroenterol Hepatol* 1998; **13**: 257-265 [PMID: 9570238 DOI: 10.1111/j.1440-1746.1998.01553.x]
- 38 **Invernizzi P**, Podda M, Battezzati PM, Crosignani A, Zuin M, Hitchman E, Maggioni M, Meroni PL, Penner E, Wiesierska-Gadek J. Autoantibodies against nuclear pore complexes are associated with more active and severe liver disease in primary biliary cirrhosis. *J Hepatol* 2001; **34**: 366-372 [PMID: 11322196 DOI: 10.1016/S0168-8278(00)00040-4]
- 39 **Muratori P**, Muratori L, Ferrari R, Cassani F, Bianchi G, Lenzi M, Rodrigo L, Linares A, Fuentes D, Bianchi FB. Characterization and clinical impact of antinuclear antibodies in primary biliary cirrhosis. *Am J Gastroenterol* 2003; **98**: 431-437 [PMID: 12591064 DOI: 10.1111/j.1572-0241.2003.07257.x]
- 40 **Wesierska-Gadek J**, Penner E, Battezzati PM, Selmi C, Zuin M, Hitchman E, Worman HJ, Gershwin ME, Podda M, Invernizzi P. Correlation of initial autoantibody profile and clinical outcome in primary biliary cirrhosis. *Hepatology* 2006; **43**: 1135-1144 [PMID: 16628641 DOI: 10.1002/hep.21172]
- 41 **Nakamura M**, Shimizu-Yoshida Y, Takii Y, Komori A, Yokoyama T, Ueki T, Daikoku M, Yano K, Matsumoto T, Migita K, Yatsuhashi H, Ito M, Masaki N, Adachi H, Watanabe Y, Nakamura Y, Saoshiro T, Sodeyama T, Koga M, Shimoda S, Ishibashi H. Antibody titer to gp210-C terminal peptide as a clinical parameter for monitoring primary biliary cirrhosis. *J Hepatol* 2005; **42**: 386-392 [PMID: 15710222 DOI: 10.1016/j.jhep.2004.11.016]
- 42 **Nakamura M**, Takii Y, Ito M, Komori A, Yokoyama T, Shimizu-Yoshida Y, Koyabu M, Matsuyama M, Mori T, Kamihira T, Daikoku M, Migita K, Yatsuhashi H, Nozaki N, Shimoda S, Ishibashi H. Increased expression of nuclear envelope gp210 antigen in small bile ducts in primary biliary cirrhosis. *J Autoimmun* 2006; **26**: 138-145 [PMID: 16337775 DOI: 10.1016/j.jaut.2005.10.007]
- 43 **Bernstein RM**, Neuberger JM, Bunn CC, Callender ME, Hughes GR, Williams R. Diversity of autoantibodies in primary biliary cirrhosis and chronic active hepatitis. *Clin Exp Immunol* 1984; **55**: 553-560 [PMID: 6368058]
- 44 **Szosteki C**, Krippner H, Penner E, Bautz FA. Autoimmune sera recognize a 100 kD nuclear protein antigen (sp-100). *Clin Exp Immunol* 1987; **68**: 108-116 [PMID: 3308206]
- 45 **Wichmann I**, Montes-Cano MA, Respaldiza N, Alvarez A, Walter K, Franco E, Sanchez-Roman J, Núñez-Roldán A. Clinical significance of anti-multiple nuclear dots/Sp100 autoantibodies. *Scand J Gastroenterol* 2003; **38**: 996-999 [PMID: 14531539]
- 46 **Worman HJ**, Courvalin JC. Antinuclear antibodies specific for primary biliary cirrhosis. *Autoimmun Rev* 2003; **2**: 211-217 [PMID: 12848948 DOI: 10.1016/S1568-9972(03)00013-2]
- 47 **Bogdanos DP**, Baum H, Butler P, Rigopoulou EI, Davies ET, Ma Y, Burroughs AK, Vergani D. Association between the primary biliary cirrhosis specific anti-sp100 antibodies and recurrent urinary tract infection. *Dig Liver Dis* 2003; **35**: 801-805 [PMID: 14674671 DOI: 10.1016/S1590-8658(03)00466-3]
- 48 **Miyachi K**, Matsushima H, Hankins RW, Hirakata M, Mimori T, Hosaka H, Amagasaki Y, Miyakawa H, Kako M, Shibata M, Onozuka Y, Ueno U. A novel antibody directed against a three-dimensional configuration of a 95-kDa protein in patients with autoimmune hepatic diseases. *Scand J Immunol* 1998; **47**: 63-68 [PMID: 9467660 DOI: 10.1046/j.1365-3083.1998.00262.x]
- 49 **Miyachi K**, Hirano Y, Horigome T, Mimori T, Miyakawa H, Onozuka Y, Shibata M, Hirakata M, Suwa A, Hosaka H, Matsushima S, Komatsu T, Matsushima H, Hankins RW, Fritzler MJ. Autoantibodies from primary biliary cirrhosis patients with anti-p95c antibodies bind to recombinant p97/VCP and inhibit in vitro nuclear envelope assembly. *Clin Exp Immunol* 2004; **136**: 568-573 [PMID: 15147362 DOI: 10.1111/j.1365-2249.2004.02456.x]
- 50 **Miyachi K**, Hosaka H, Nakamura N, Miyakawa H, Mimori T, Shibata M, Matsushima S, Chinoh H, Horigome T, Hankins RW, Zhang M, Fritzler MJ. Anti-p97/VCP antibodies: an autoantibody marker for a subset of primary biliary cirrhosis patients with milder disease? *Scand J Immunol* 2006; **63**: 376-382 [PMID: 16640662 DOI: 10.1111/j.1365-3083.2006.01747.x]
- 51 **Takiguchi J**, Ohira H, Rai T, Abe K, Takahashi A, Sato Y. Anti-eosinophil peroxidase antibodies detected in patients with primary biliary cirrhosis. *Hepatol Res* 2005; **32**: 33-37 [PMID: 15908264 DOI: 10.1016/j.hepres.2005.01.013]
- 52 **Zachou K**, Liaskos C, Rigopoulou E, Gabeta S, Papamichalis P, Gatselis N, Georgiadou S, Dalekos GN. Presence of high avidity anticardiolipin antibodies in patients with autoimmune cholestatic liver diseases. *Clin Immunol* 2006; **119**: 203-212 [PMID: 16500150 DOI: 10.1016/j.clim.2006.01.002]
- 53 **Gabeta S**, Norman GL, Gatselis N, Liaskos C, Papamichalis PA, Garagounis A, Zachou K, Rigopoulou E, Dalekos GN. IgA anti-b2GPI antibodies in patients with autoimmune liver diseases. *J Clin Immunol* 2008; **28**: 501-511 [PMID: 18551357 DOI: 10.1007/s10875-008-9211-6]
- 54 **Muratori P**, Muratori L, Guidi M, Maccariello S, Pappas G, Ferrari R, Gionchetti P, Campieri M, Bianchi FB. Anti-Saccharomyces cerevisiae antibodies (ASCA) and autoimmune liver diseases. *Clin Exp Immunol* 2003; **132**: 473-476 [PMID: 12780695 DOI: 10.1046/j.1365-2249.2003.02166.x]
- 55 **Sakly W**, Jeddi M, Ghedira I. Anti-Saccharomyces cerevisiae antibodies in primary biliary cirrhosis. *Dig Dis Sci* 2008; **53**: 1803-1807 [PMID: 18049897 DOI: 10.1007/s10620-007-0092-y]
- 56 **Fagoonee S**, De Luca L, De Angelis C, Castelli A, Rizzetto M, Pellicano R. Anti-Saccharomyces cerevisiae as unusual antibodies in autoimmune hepatitis. *Minerva Gastroenterol Dietol* 2009; **55**: 37-40 [PMID: 19212306]

- 57 **Mayo I**, Arizti P, Parés A, Oliva J, Doforno RA, de Sagarra MR, Rodés J, Castaño JG. Antibodies against the COOH-terminal region of E. coli ClpP protease in patients with primary biliary cirrhosis. *J Hepatol* 2000; **33**: 528-536 [PMID: 11059856 DOI: 10.1016/S0168-8278(00)80003-3]
- 58 **Bogdanos DP**, Baum H, Sharma UC, Grasso A, Ma Y, Burroughs AK, Vergani D. Antibodies against homologous microbial caseinolytic proteases P characterise primary biliary cirrhosis. *J Hepatol* 2002; **36**: 14-21 [PMID: 11804659 DOI: 10.1016/S0168-8278(01)00252-5]
- 59 **Roesler KW**, Schmider W, Kist M, Batsford S, Schiltz E, Oelke M, Tuczek A, Dettenborn T, Behringer D, Kreisel W. Identification of beta-subunit of bacterial RNA-polymerase-a non-species-specific bacterial protein--as target of antibodies in primary biliary cirrhosis. *Dig Dis Sci* 2003; **48**: 561-569 [PMID: 12757171]
- 60 **Muratori P**, Granito A, Pappas G, Pendino GM, Quarneri C, Cicola R, Menichella R, Ferri S, Cassani F, Bianchi FB, Lenzi M, Muratori L. The serological profile of the autoimmune hepatitis/primary biliary cirrhosis overlap syndrome. *Am J Gastroenterol* 2009; **104**: 1420-1425 [PMID: 19491855 DOI: 10.1038/ajg.2009.126]
- 61 **Subasić D**, Karamehić J, Ljuca F, Gavrankapetanović F, Delić-Sarac M, Eminović I, Kovacević D. Correlation of autoantibodies presence detected by IFA-anti-dsDNA, IFA-AMA and immunoblotting with corresponding data in clinical management of autoimmune diseases. *Bosn J Basic Med Sci* 2008; **8**: 86-92 [PMID: 18318679]
- 62 **Agmon-Levin N**, Shapira Y, Selmi C, Barzilai O, Ram M, Szyper-Kravitz M, Sella S, Katz BS, Youinou P, Renaudineau Y, Larida B, Invernizzi P, Gershwin ME, Shoenfeld Y. A comprehensive evaluation of serum autoantibodies in primary biliary cirrhosis. *J Autoimmun* 2010; **34**: 55-58 [PMID: 19897339 DOI: 10.1016/j.jaut.2009.08.009]
- 63 **Tishler M**, Alosachie I, Barka N, Lin HC, Gershwin ME, Peter JB, Shoenfeld Y. Primary Sjögren's syndrome and primary biliary cirrhosis: differences and similarities in the autoantibody profile. *Clin Exp Rheumatol* 1995; **13**: 497-500 [PMID: 7586784]
- 64 **Granito A**, Muratori P, Muratori L, Pappas G, Cassani F, Worthington J, Ferri S, Quarneri C, Cipriano V, de Molo C, Lenzi M, Chapman RW, Bianchi FB. Antibodies to SS-A/Ro-52kD and centromere in autoimmune liver disease: a clue to diagnosis and prognosis of primary biliary cirrhosis. *Aliment Pharmacol Ther* 2007; **26**: 831-838 [PMID: 17767467 DOI: 10.1111/j.1365-2036.2007.03433.x]
- 65 **Fusconi M**, Vannini A, Dall'Aglio AC, Pappas G, Cassani F, Ballardini G, Frisoni M, Grassi A, Bianchi FB, Zauli D. Anti-cyclic citrullinated peptide antibodies in type 1 autoimmune hepatitis. *Aliment Pharmacol Ther* 2005; **22**: 951-955 [PMID: 16268969 DOI: 10.1111/j.1365-2036.2005.02686.x]
- 66 **Santiago M**, Baron M, Miyachi K, Fritzler MJ, Abu-Hakima M, Leclercq S, Bell M, Hudson M, Mathieu JP, Taillefer S, Jones N, Docherty P, Khraishi M, Markland J, Pope J, Robinson D, Smith D, Sutton E. A comparison of the frequency of antibodies to cyclic citrullinated peptides using a third generation anti-CCP assay (CCP3) in systemic sclerosis, primary biliary cirrhosis and rheumatoid arthritis. *Clin Rheumatol* 2008; **27**: 77-83 [PMID: 17570008 DOI: 10.1007/s10067-007-0656-4]
- 67 **Koga T**, Migita K, Miyashita T, Maeda Y, Nakamura M, Abiru S, Myoji M, Komori A, Yano K, Yatsuhashi H, Eguchi K, Ishibashi H. Determination of anti-cyclic citrullinated peptide antibodies in the sera of patients with liver diseases. *Clin Exp Rheumatol* 2008; **26**: 121-124 [PMID: 18328158]
- 68 **Saito H**, Takahashi A, Abe K, Okai K, Katsushima F, Monoe K, Kanno Y, Ohira H. Autoantibodies by line immunoassay in patients with primary biliary cirrhosis. *Fukushima J Med Sci* 2012; **58**: 107-116 [PMID: 23237866 DOI: 10.5387/fms.58.107]

P- Reviewers: He XS, Hua J, Jin S S- Editor: Wen LL
L- Editor: A E- Editor: Ma S





百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**

Flat C, 23/F., Lucky Plaza,

315-321 Lockhart Road, Wan Chai, Hong Kong, China

Fax: +852-65557188

Telephone: +852-31779906

E-mail: bpgoffice@wjgnet.com

<http://www.wjgnet.com>



ISSN 1007-9327



9 771007 932045