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Concise reviews

Anti-gp210-positive primary biliary cholangitis: The dilemma of clinical treatment and emerging mechanisms

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ABSTRACT

Anti-gp210 is the disease-specific anti-nuclear antibody (ANA) of primary biliary cholangitis (PBC). Anti-gp210-positive PBC patients have worse responses to ursodeoxycholic acid (UDCA) as compared with anti-gp210-negative patients. Moreover, anti-gp210-positive patients always present with more severe histopathologic features including lobular inflammation, interfacial hepatitis, and bile duct injury, and have a worse prognosis than their anti-gp210-negative counterparts. Previous studies have identified two antigenic epitopes recognized by anti-gp210. Although the pathogenetic mechanism of anti-gp210 production remains unclear, evidence suggests that the autoimmune response to anti-gp210 production might be due to molecular mimicry induced by bacteria or endogenous peptides. T cells and related cytokines play a critical role in the pathogenesis of PBC, however, the mechanism hasn't been fully understood. Thus, this review focuses on the clinicopathological characteristics of anti-gp210-positive PBC patients, the fundamental research of gp210 antigen, and the possible mechanism of anti-gp210 production to clarify the mechanism of anti-gp210-positive PBC and provide potential molecular targets for disease prevention and treatment in the future.

1. Introduction

Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune liver disease characterized by non-suppurative inflammation of small- and medium-sized bile ducts in the liver, which causes cirrhosis. Serum antimitochondrial antibody (AMA) is the major hallmark of PBC [1]. However, AMA is absent or present only in low titers in approximately 5%–10% of PBC patients [2]. More than 30% of AMA-negative PBC patients have PBC-specific anti-nuclear antibodies (ANA), including anti-gp210 and anti-sp100 antibodies [3]. Moreover, anti-gp210 can be detected in 13.8%–48.2% of PBC patients, with high specificity (>98%) for the diagnosis [4–17]. Since 2017, anti-gp210 has become a diagnostic marker for the diagnosis of AMA-negative PBC, improving the diagnostic rate and thus avoiding unnecessary liver biopsy in some patients [2,18].

Anti-gp210 is not only a highly specific antibody for the diagnosis of PBC but also a prognostic marker. Anti-gp210-positive PBC patients had worse responses to ursodeoxycholic acid (UDCA) (39.3% vs. 16.7%), higher levels of biochemical liver tests, more severe histopathological presentation, and worse prognosis as compared to anti-gp210-negative patients [4-6,19]. The therapeutic effects of different drugs, including obeticholic acid (OCA), fibrates, glucocorticoids, and immunosuppressants in anti-gp210-positive and -negative PBC patients have been compared, and it has been found positivity remains a risk factor for poor treatment response [8,19]. Thus, anti-gp210 is a risk factor for poor response to UDCA and poor prognosis in PBC patients, and thus clarifying the production of anti-gp210 and its mechanism in PBC is very important for the development of effective therapeutic targets.

Currently, studies on the molecular mechanisms of anti-gp210 in PBC are still limited. The antigen of anti-gp210 is gp210, one of the constitutive proteins of the nuclear pore complex [20]. Two antigenic epitopes of gp210 protein have been identified, which laid a theoretical basis for the detection of anti-gp210 and the exploration of antigen expression as well as antibody production [21,22]. Notably, Nickowitz *et al.* [6] found that the gp210 expression in biliary epithelial cells (BECs) in the liver of PBC patients was significantly increased compared to that in the patients of AIH and hepatitis C, however, it

Abbreviations: PBC, Primary biliary cholangitis; AMA, antimitochondrial antibody; ANA, anti-nuclear antibodies; UDCA, ursodeoxycholic acid; OCA, obeticholic acid; BECs, biliary epithelial cells; AST, aspartate aminotransferase; ALP, alkaline phosphatase; IgM, immunoglobulin M; GWAS, genome-wide association studies; HLA, human leukocyte antigen; SNP, single-nucleotide polymorphism

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did not correlate with the production of anti-gp210 antibody. Thus, it is suggested that gp210 antigen may be involved in the bile duct injury of PBC. In addition, in terms of the potential mechanism for anti-gp210 production, molecular mimicry is the major hypothesis at present [21]. However, whether or not anti-gp210 is directly involved in the occurrence and development of PBC still requires more exploration or merely represents epiphenomenon. Collectively, the clinicopathological characteristics of anti-gp210-positive PBC patients, the production of anti-gp210 antibodies, and the possible pathogenic mechanism are reviewed to deeply understand the role of anti-gp210 in PBC.

2. Anti-gp210-positive PBC patients have poor treatment response and prognosis

Anti-gp210-positive PBC patients have a lower UDCA response rate than their anti-gp210-negative counterparts. In a cohort of 499 PBC patients from the UK, Haldar et al. [4] reported that anti-gp210-positive patients treated with UDCA did not respond sufficiently to treatment as compared to anti-gp210-negative patients (39.3% vs. 16.7%). The study further confirmed that anti-gp210 could be used as an index to predict poor response to UDCA treatment, with sensitivity and specificity of 26.8% and 89.8%, respectively. Chen Q *et al.* [23] conducted a retrospective cohort study of 180 UDCA-treated Chinese PBC patients to assess the prognostic value of anti-gp210 and found that positivity for anti-gp210 was independently associated with a higher risk of liver-related death and transplantation. In summary, anti-gp210-positive PBC patients have low UDCA response rates and poor prognosis.

Second-line therapeutic drugs, such as OCA, fibrates, and corticosteroids are available for UDCA-refractory PBC patients, however, the treatment efficacy remains unsatisfactory for anti-gp210-positive patients. Nakamura *et al.* [8] enrolled 50 and 114 anti-gp210-positive and -negative PBC patients, respectively, (115 PBC patients of UDCA monotherapy and 49 UDCA-refractory PBC patients of UDCA combined with prednisolone and/or bezafibrate) in a retrospective study. This study showed that the liver function of both groups had improved after 2 years of treatment, however, anti-gp210-positive patients presented with higher levels of aspartate aminotransferase (AST), alkaline phosphatase (ALP), and immunoglobulin M (IgM) after treatment than anti-gp210-negative patients. Then, Qian *et al.* [19] respectively compared the responses of 29 and 51 anti-gp210-positive and -negative PBC patients who received UDCA or UDCA, prednisolone, and immunosuppressant (AZA or MMF) triple therapy, and reported that the incidence of poor prognosis (such as increasing rate of PBC related complications, liver transplantation, and mortality) was higher in anti-gp210-positive PBC patients than in anti-gp210-negative patients.

Anti-gp210 is closely associated with poor prognosis in PBC patients. In 1998, Itoh *et al.* [11] initially reported that anti-gp210-positive PBC patients had a three times higher mortality rate (40.0% vs. 13.6%), and 3.5 times higher probability of death from liver failure (32.0% vs. 9.1%) than anti-gp210-negative patients. The liver transplantation free survival time of anti-gp210-positive PBC patients was significantly shorter than their anti-gp210-negative PBC counterparts. Meanwhile, Yang F *et al.* [7] found that anti-gp210-positive patients had remarkably higher UK-PBC scores and poorer long-term prognoses than anti-gp210-negative patients. Previous investigators have reported that the presence of fatigue and pruritus during diagnosis is associated with poor responsiveness to UDCA treatment, and more inclined to evolve to cirrhosis and its complications in PBC [24]. Thus, anti-gp210 may help together with clinical features to identify the subgroup of PBC patients with more severe prognoses.

Nakamura M *et al.* [25] further studied the relationship between the titer of anti-gp210 and disease severity and prognosis. They found that patients with reduced anti-gp210 titers showed milder disease and better prognosis than patients whose anti-gp210 titers were unchanged or elevated after UDCA treatment [5]. Furthermore, they concluded that the change of anti-gp210 titers in serum had great significance for the prognosis of the disease [5]. However, the issue of whether or not the titer of anti-gp210 is variable remains controversial because some studies have pointed out that anti-gp210 titers in PBC patients did not change over a long follow-up period of 3–10 years [11,12]. Therefore, we summarized the detection methods, substrates, and the changes of anti-gp210's serum antibody titers in previous studies to figure out why those research results differ (Table 1) [5,8,11-13]. We found that the change of antibody titer can be detected when the carboxy-terminal tail of gp210 was used as the detection substrate, whereas the studies reporting that the titer was unchanged did not indicate what detection substrate was used. Therefore, we speculated that the variability of anti-gp210 titers is related to different substrates in antibody detection. Currently, UDCA-refractory anti-gp210-positive PBC patients lack effective therapeutic strategies and have worse prognoses as compared to anti-gp210-negative patients. Thus, exploring new therapeutic targets is urgently needed.

3. Anti-gp210-positive PBC patients have severe biochemical liver tests and histological indexes

In biochemical liver tests, anti-gp210-positive PBC patients have higher levels of ALP, bilirubin, globulin and IgM than their anti-gp210-negative counterparts. In 1998, Itoh *et al.* [11] compared the biochemical liver tests in 25 and 88 anti-gp210-positive and -negative PBC patients at the first diagnosis, respectively, and found that the levels of ALT and total bilirubin were significantly higher in anti-gp210-positive PBC patients than that in anti-gp210-negative patients. Subsequently, anti-gp210-positive PBC patients had significantly higher liver biochemical and immunological indicators than their anti-gp210-negative counterparts (Table 2) [4,5,7,11,12,17]. Therefore, anti-gp210-positive PBC patients had higher serum levels of bile duct injury-related indicators at the initial diagnosis as compared with anti-gp210-negative patients, thereby suggesting more severe bile duct injury at the early stage of the disease.

Currently, the histological studies of anti-gp210 related are limited. Nakamura *et al.* [5] enrolled 23 anti-gp210-positive PBC

Table 1
The substrate used in detection anti-gp210 and the variability of anti-gp210.

Methods of detection	Time	Country of cases	Detection of substrate	Variable titers (Follow up number)	Follow up time (month/year)
IIF (Rim-like)	1998 [11]	Japan	HepG2 cells	NO (10)	87.5 ± 56.0 m
	2003 [12]	Italy	HEp-2 cell lines	Not investigated	–
ELISA	2003 [12]	Italy	Purified gp210 ELISA kits (IMTEC)	NO (6)	3–10 y
	2005 [5]	Japan	gp210 C-terminal peptide	YES (23)	73.4 ± 54.3 m
	2007 [13]	Japan	gp210 C-terminal peptide (25 amino acids)	YES (217)	1–292 m
	2014 [8]	Japan	gp210 C-terminal peptide (25 amino acids)	YES (50)	6–12 m

IIF, indirect immunofluorescence; ELISA, enzyme-linked immunosorbent assay; IB, immunoblot.

Table 2
Biochemical liver Indicators of anti-gp210-positive PBC patients are higher than anti-gp210-negative PBC patients.

Clinical research	Time	Country	Number of patients% (gp210+/PBC)	Indicators with statistical difference
Itoh S et al. [11]	1998	Japan	22.1 (25/113)	ALP, TBIL
Paolo et al. [12]	2003	Italy	15.6 (15/96)	ALP, GGT, TC, ALB, γ-GLB, IgA, IgM
Minoru et al. [5]	2005	Japan	32.4 (23/71)	IgM
Dimitrioa et al. [17]	2007	Spain and Greece	10.5 (38/362)	ALP, DBIL
Yang et al. [7]	2017	China	48.2 (133/276)	GGT, TBIL
Haldar et al. [4]	2021	UK	16.7 (81/486)	AST, ALT, TBIL

TP, total protein; ALB, albumin; GLB, globulin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; TBIL, total bilirubin; DBIL, direct bilirubin; TC, total cholesterol; Ig, immunoglobulin; Plt, platelet.

patients and found that anti-gp210 titers were sustained at high levels in 10 patients after UDCA treatment, and showed more severe interface hepatitis and higher activity score than the patients with reduced titer. Subsequently, Nakamura *et al.* [6] had done immunohistochemical staining using gp210 monoclonal antibody in the liver tissue, and for the first time, they proposed that the expression of gp210 antigen was increased on the nuclear envelope of BECs of small bile ducts in PBC patients as compared to healthy controls. Furthermore, in this study, gp210 immunostained BECs were generally surrounded by inflammatory cells or fibrous tissues, and the degree of gp210 expression was positively correlated with portal inflammation, interface hepatitis, and lobular inflammation, thereby suggesting that the expression of gp210 antigen may be involved in the chemotactic process of lymphocytes infiltrating to BECs in PBC. However, there was no correlation between the high expression of gp210 antigen in the BECs and the positivity of anti-gp210 in the serum, thus further studies are needed to elucidate the relationship between the gp210 antigen production in BECs and anti-gp210 production in serum.

4. Molecular structures of anti-gp210 and gp210 antigen and the application in PBC

Anti-gp210 is a reliable indicator for the diagnosis of PBC. The anti-gp210 positivity rates were 14.3%–48.2% and 15.4%–46.7% in PBC patients and AMA-negative PBC patients, with specificity of over 99% and sensitivity of approximately 25% [4–17,24]. The study addressing the diagnostic accuracy of anti-gp210 for PBC diagnosis was performed in more than 4000 sera from patients suspected of having liver and non-liver autoimmune and non-autoimmune diseases, thereby demonstrating a very high specificity and positive predictive value for the diagnosis of PBC [26]. This suggests that anti-gp210 is highly correlated with the pathogenesis of PBC.

In 1985, Ruffati *et al.* [20] discovered that anti-gp210 was an antinuclear membrane antibody that labeled the nucleus of Hep-2 cells with a rim-like pattern. The anti-gp210 antibody belonged to IgG, a specific antibody against the antigens including DNase I, RNase, and trypsin [27,28]. The sensitivity of anti-gp210 and the corresponding immunofluorescence pattern is higher when the detection of autoantibodies is performed at the level of IgG isotype (in particular IgG1 isotype) because it determines a wide gain in terms of sensitivity without a loss of specificity [29]. Anti-gp210 has high specificity but low sensitivity for the diagnosis of PBC. Therefore, other antinuclear antibodies in AMA -negative PBC cases are been investigated. Antibodies to hexokinase 1 (HK1) and kelch-like 12 (KLHL12) were described as additional biomarkers in these patients [30,31].

Gp210 protein can be found in most nucleus cells, located on the nuclear membrane as one of the constituent proteins of the nuclear pore complex. Gp210 is a 210 kDa type I integral membrane protein that assembles nuclear pore protein after mitosis and fixes nuclear pore complex to the pore membrane. More importantly, gp210 protein mediates nuclear pore expansion and macromolecular transport between the nucleus and the cytoplasm [32]. In addition, gp210 consists of three domains, including a 1808 amino acid amino-terminal domain situated in the perinuclear space, a 20 amino acid transmembrane segment, and a 58 amino acid carboxy-terminal tail domain (Fig. 1) [33,34]. Collectively, these studies elucidated the localization, function, and structure of the gp210 antigen, thereby laying the foundation for the subsequent antibody detection and the production mechanism of anti-gp210.

Regarding the antigen-antibody interaction, two gp210 epitopes have been identified by serum anti-gp210 of PBC patients. One is the 15 amino acids located at the carboxy-terminal tail and the other one is in the glycosylation regions at the amino-terminal domain [21,22]. Thus, these two structural regions are important molecular regions to study gp210 and anti-gp210 as well as their roles in PBC. In 1993, Nickowitz *et al.* [21] detected serum antibodies of 25 anti-gp210-positive PBC patients using bacterial gp210 fusion proteins and demonstrated that 15 amino acids in the carboxy-terminal tail domain between 1869 and 1883 can bind to anti-gp210. Subsequently, Bandin O *et al.* [16] demonstrated that 97.2% (70/72) of the serum antibodies of anti-gp210-positive PBC patients identified the same carboxy-terminal epitope. Thus, the carboxy-terminal epitope of gp210 protein has been widely recognized in previous studies. Moreover, Wesierska-Gadek *et al.* [22] confirmed that the recognition epitopes to anti-gp210 existed in the glycosylation domain of the amino-terminal of gp210. In this study, 12 anti-gp210-positive PBC patients were enrolled, and antibodies against an epitope within the glycosylation domain of the amino-terminal and in the carboxy-terminal tail were detected in the sera of 8 and 4 patients, respectively. Howeve, the above studies suggest that the detection of antibodies with bacterial gp210 fusion proteins has certain limitations. Therefore, in the future, it is necessary to develop a detection kit for dual epitopes of anti-gp210 and explore additional detection sites to improve the sensitivity of antibody detection and avoid the delay of diagnosis and timely treatment in PBC patients.

5. Pathogenesis of anti-gp210-positive PBC patients

The rate of anti-gp210 positivity among PBC patients in different studies varies in different countries and human species (Table 3) [4–16]. The detection rate of anti-gp210 in Chinese and German is higher than that in other countries, ranging from 35.7% to 48.2%. This difference suggests that genetic and environmental factors play an important role in the production of anti-gp210 in PBC.

However, the mechanism of anti-gp210 in the development of PBC remains unclear. Regarding genetics, Wang *et al.* [14] conducted genome-wide association studies (GWAS) in 930 Chinese PBC patients based on their autoantibody status (anti-gp210 and anti-sp100), of which 350/912 (38.4%) were anti-gp210-positive patients, and no specific human leukocyte antigen (HLA) allele or single-nucleotide polymorphism (SNP) associated with anti-gp210 was found. In terms of environmental factors, Tang R *et al.* [35] analyzed the gut

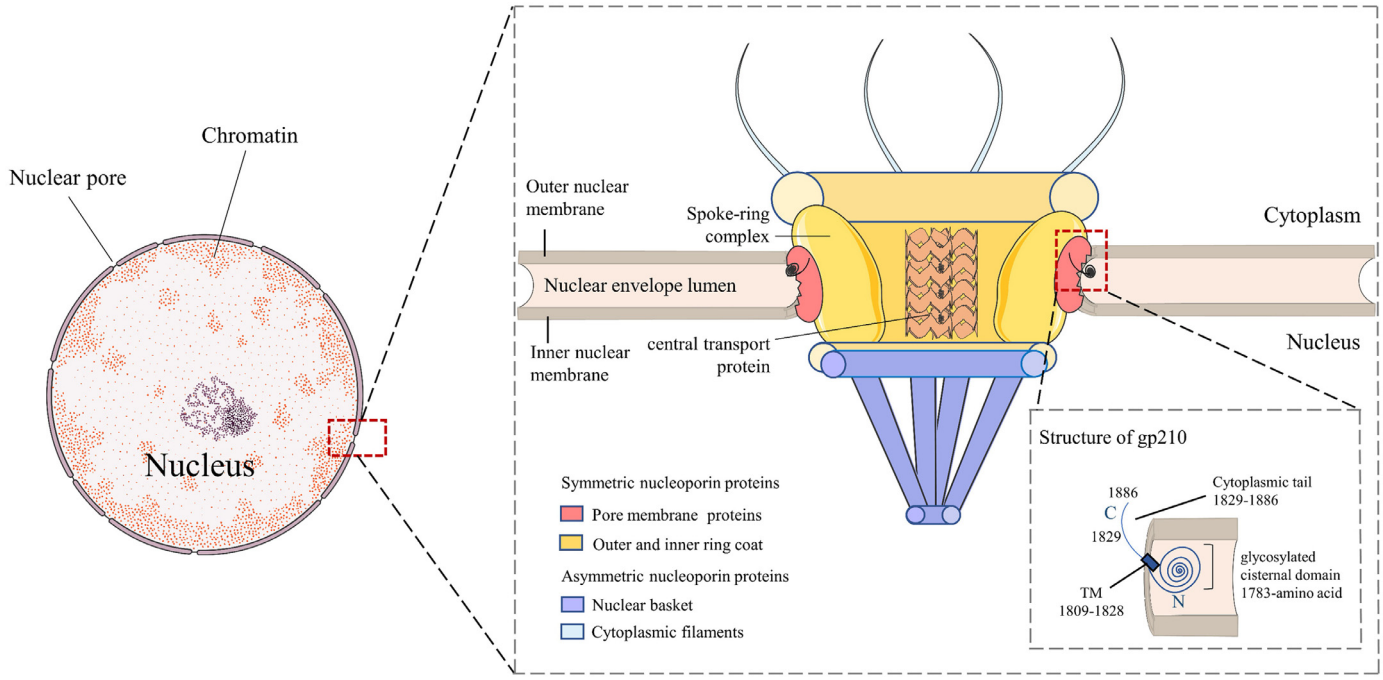

Fig. 1. The structural diagram of nuclear pore membrane protein gp210.

microbiome of 116 Chinese PBC patients and found that the gut microbiome of anti-gp210-positive patients showed relatively lower species richness and *Faecalibacterium spp* abundance than the anti-gp210-negative patients, thereby indicating that the gut microbiota may play a role in the pathogenesis of anti-gp210-positive PBC patients.

Therefore, for the epitopes of anti-gp210 to be deeply investigated, some studies have found that molecular mimicry, induced by proteins with similar amino acid sequences to epitopes, may be one of the main mechanisms in anti-gp210 production. Molecular mimicry is the process by which exogenous antigens activate autoreactive T or B cells in susceptible individuals because of the similarity between exogenous peptides and self-peptides [36]. Before the 1990s, the transmembrane topology of gp210 closely resembled the envelope glycoproteins topology of various animal viruses [37–39]. Subsequently, Nickowitz *et al.* [21] demonstrated that the cytoplasmic carboxy-terminal tail epitope of anti-gp210 had six consecutive amino acids which were homologous to the protein products of the *Escherichia coli mutY* and *Salmonella typhimurium mutB* genes. In addition, Haruta *et al.* [40] found that *Streptococcus intermedius* (*S.i.*) could induce the generation of anti-gp210 and cellular infiltration around the bile ducts in BALB/c mice. Moreover, the antibody against histone-like DNA-binding protein of *Streptococcus intermedius* (*S.i.*-HLP) could bind to synthetic gp210 peptide. Thus, these studies suggest that bacteria or viruses may induce the production of anti-gp210 through molecular mimicry (Fig. 2). Clinical studies also found that anti-gp210 could persist for more than 10 years after liver transplantation in some PBC patients [9–11], thereby further suggesting that the antigen inducing the generation of anti-gp210 might not be derived from the liver. Bacteria-induced molecular mimicry in the production of anti-gp210 may provide new insights into the pathogenesis of anti-gp210-positive PBC patients. In addition to exogenous peptides such as bacteria and viruses, molecular mimicry exists between endogenous peptides such as mitochondria and gp210 in PBC. Shimoda *et al.* [41] discovered that the selected specific T cell clones of a peptide corresponding to the mitochondrial pyruvate

Table 3
The positive rate of anti-gp210 in PBC patients in different countries.

Methods of detection	Time	Country of cases	Positivity% (Anti-gp210+/PBC)	Positivity% (Anti-gp210+/AMA- PBC)
IIF (Rim-like)	1996 [16]	France	30.5 (87/285)	46.7 (7/15)
	1998 [11]	Japan	27.4 (31/113)	18.2 (2/11)
	2003 [12]	Italy	10.0 (9/91)	33.0 (5/19)
ELISA	1996 [16]	France	25.5 (73/285)	46.8 (7/15)
	2003 [12]	Italy	16.0 (15/96)	15.4 (2/13)
	2005 [5]	Japan	32.4 (23/71)	–
	2006 [6]	Japan	38.5 (20/52)	–
	2007 [13]	Japan	26.1 (72/276)	–
	2014 [8]	Japan	30.5 (50/164)	
	2019 [14]	China	38.4 (350/912)	–
IB	1996 [16]	France	25.3 (72/285)	–
	1997 [10]	USA	25.7 (9/35)	–
	1998 [11]	Japan	22.1 (25/113)	20.0 (1/5)
	1998 [9]	Germany	35.7 (15/42)	–
	2003 [12]	Japan	26.3 (46/175)	18.5 (10/54)
	2003 [15]	Japan	28.2 (46/163)	–
	2017 [7]	China	48.2 (133/276)	41.2 (7/17)
	2021 [4]	UK	16.7 (81/486)	16.9 (12/72)

IIF, indirect immunofluorescence; ELISA, enzyme-linked immunosorbent assay; IB, immunoblot.

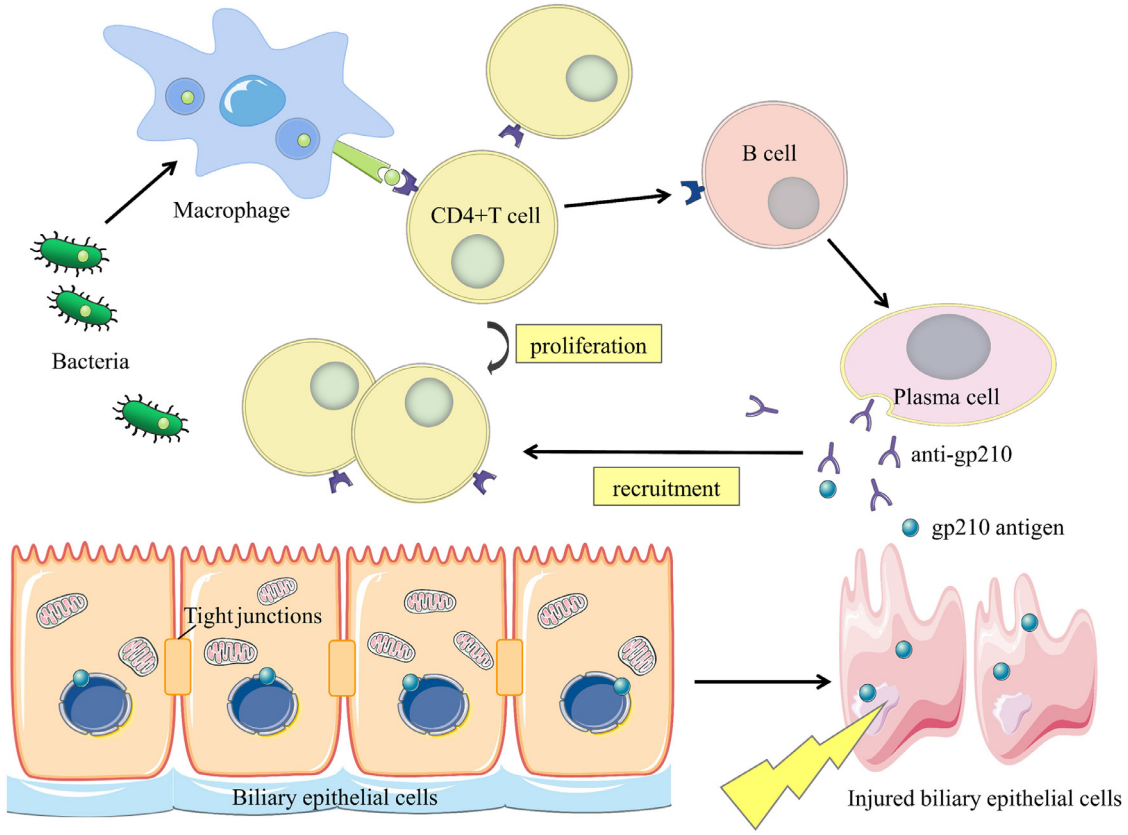

Fig. 2. The simulation diagram of bacterial induction of anti-gp210 through molecular mimicry.

dehydrogenase complex E2 subunit could cross-react with the synthetic peptide of gp210, thereby indicating a possible cross pathway existed between AMA and the production process of anti-gp210. Furthermore, T cell clones selected by recombinant gp210 protein simultaneously reacted with the mimicry peptide of amino acid 188–201 in gp210, thereby indicating that the amino acid 188–201 in gp210 was one of the immunodominant T cell epitopes.

Current research on the relationship between anti-gp210 and the pathogenesis of PBC is very limited. Notably, anti-gp210 can be detected in the serum of the dominant-negative form of TGF-β receptor type II (dnTGF-βRII) mice, one of the main model mice of PBC. In addition, Yang CY *et al.* [42] found that the titer of anti-gp210 was significantly reduced by deleting specific cytokines (including IL-12p40, IL-23p19, IL-17, IL-6, and TNF-α) in dnTGF-βRII mice, thereby suggesting that these cytokines may be involved in the production of anti-gp210. In recent years, studies on immune cells and the pathogenesis of PBC are actively underway, and thus clarifying the pathogenesis of anti-gp210-positive PBC is essential to explore new therapeutic intervention targets for these patients. Collectively, current research on the pathogenesis of anti-gp210-positive PBC primarily focuses on aspects including genetic and environmental factors, molecular mimicry, and cytokines. Therefore, an in-depth investigation of the interrelationship among the above three aspects could provide direction for further study on anti-gp210-positive PBC.

6. Discussion and prospect

Anti-gp210-positive PBC patients present with more severe biochemical indexes, severe bile duct injury and liver inflammation in histology, poorer response to treatment drugs, faster disease progression, and a worse prognosis than anti-gp210-negative patients. It is of clinical importance to identify the pathogenesis of anti-gp210-positive PBC and find preventive measures against the etiology to guide the diagnosis and treatment of the disease.

7. Conclusions

Anti-gp210 is an autoantibody against the nuclear membrane protein gp210, and thus the study of anti-gp210 and the antigen is essential for the pathogenesis of anti-gp210-positive PBC. Moreover, the species richness of gut microbiome in anti-gp210-positive PBC patients was lower than that in anti-gp210-negative patients, thereby suggesting that intestinal microecology may participate in disease development and progression. Molecular mimicry by bacteria is currently the main hypothesis for the pathogenesis, which still needs to be further explored. The study on the localization, structure, and epitope of gp210 antigen has laid a certain theoretical foundation for the study of anti-gp210-positive PBC pathogenesis. With the development of epidemiology, genetics, and animal models, further elucidation of the generation and molecular mechanism of anti-gp210 in PBC will be crucial for clinical prevention and treatment.

Declaration of interests

None.

Author contributions

Xiaoyi Wang and Zhen Yang searched literatures, Xiaoyi Wang, Zhen Yang and Ying Ran drafted the manuscript, Long Li, Bangmao Wang and Lu Zhou discussed and revised the manuscript.

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